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IMPRESSIONS OF HEMATODYSCRASIC SURGERY

DAVID MOVITZ, M.D.*

Wider therapeutic applications of splenectomy and variations in the technique of splenectomy may be based upon a concept of hematolytopoietic equilibrium in which the quantity of cellular elements in the peripheral blood represents a balance between cellular production by the marrow and of destruction through splenic mechanisms. The underlying concepts of hematodyscrasic surgery to be here presented are outgrowths of impressions gained from an association with George M. Curtis[1, 2] in the pioneering spleen group at Ohio State University—Doan, Weisman, and Curtis.

An anemia, a leukopenia, or a thrombocytopenia or any combination of these three peripheral deficiencies when associated with normal or increased numbers of the respective precursor cells in the marrow represents a functional state generally designated as **hypersplenism.** This functional change is classified into primary and secondary hypersplenisms. **Primary** hypersplenisms are instances in which no pathic changes other than the hypersplenism are demonstrable. **Secondary** hypersplenisms are instances of hypersplenism in which another pathic change such as Hodgkin's disease or leukemia or an infectious granuloma is present in addition and is etiologically related to the hypersplenism.

Known primary hypersplenic diseases are (1) congenital hemolytic icterus, (2) primary thrombocytopenic purpura, (3) primary splenic neutropenia, and (4) pansplenic hematocytopenia. Banti's syndrone may perhaps be classified as a secondary hypersplenism. Secondary hypersplenisms as previously indicated may occur in the course of Hodgkin's disease, or of the leukemias, the lymphosarcomas, the infectious granulomas such as monilisis, tuberculosis, and in the lipid histiocytoses such as Gaucher's disease, and perhaps in some instances of portal hypertension.

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Although splenectomy for a hematodyscrasia should almost never be done without consultation of the hematologist, the surgeon, nevertheless, is responsible for the result. Inasmuch as the hypersplenic basis for splenectomy appears to have offered a reliable guide, the surgeon, therefore, should be familiar with the concepts of primary and secondary hypersplenisms, particuarly their essential diagnostic criteria. It appears vital that hypersplenism be present before splenectomy is undertaken. A striking example of this is experienced in the management of splenic thrombocytopenic purpura with hemorrhage. The result of splenectomy is usually almost immediately discernible. The splenectomy, however, is not undertaken unless megakaryocytes are demonstrated in the marrow in association with the thrombopenia. In the course of the operation, before the splenic pedicle can be clamped, profuse capillary oozing from the incisional wound edges and the other cut surfaces continues uncontrollably. Should hypersplenism not be present, e.g., as in a myelophthisic or as in a toxic thrombocytopenia purpura (i.e., without megakaryocytes in the marrow), bleeding from the "raw" surfaces will continue postoperatively, augmenting the hemorrhage which was also present preoperatively. This is tantamount to almost certain death. On the other hand, if the thrombocytopenic bleeding is hypersplenic in origin, it ceases almost immediately after splenctomy.

Hypersplenic Thromocytopenic Purpura

The diagnosis of primary thrombocytopenic purpura may be considered in patients with any or all of the following: purpura of the skin or of the visible mucous membranes, epistaxis, bleeding gums, hematuria, melena, hemarthrosis, menorrhagia, metrorrhagia, or cerebral hemorrhage. Obviously, other diseases may cause bleeding, but a deficiency in the number of platelets in the peripheral blood indicates a diagnosis of thrombo-

cytopenic purpura. If megakaryocytes are observed in the marrow, the diagnosis conforms to a hypersplenic thrombocytopenic purpura. Increased numbers of eosinophiles in addition to the megakaryocytes in the marrow may indicate an allergic thrombopenic purpura.[6] Furthermore, primary thrombocytopenic purpura is associated with a normal sized spleen. An enlarged spleen associated with the above findings is indicative of a secondary hypersplenic thrombocytopenic purpura. In instances of the secondary type, that is—with an enlarged spleen, there is present an associated disease etiologically related to the hypersplenism. The associated disease involving the spleen and also causing the secondary hypersplenism, as previously enumerated, may be Hodgkin's disease, or leukemia, or lymphosarcoma, or an infectious granuloma or a lipid histiocytosis, or a portal hypertension, or Banti's syndrome. Splenectomy is indicated in both the primary or secondary type. Obviously, the fundamental disease such as Hodgkin's disease, Gaucher's disease, or leukemia, etc., causing the secondary type, is not removed by the process of splenectomy, but the hypersplenism is alleviated.

The preoperative management of splenic thrombocytopenic purpura is a vital factor in determining the survival or death of the patient. A most important decision is to determine the time for splenectomy. In the presence of active bleeding, splenectomy is an immediate emergency—emphatically, even at 3 a.m. First, of course, the hematologist must accurately diagnose, with bone marrow study even at 2 a.m. Delay at this time frequently results in the death of the patient. The most common cause is cerebral hemorrhage, and frequently occurs in the interval between the time of diagnosis and the next regular operative schedule. Otherwise death may result simply from exsanguination. On the other hand, immediate splenectomy is dramatically effective.

Since platelets in vitro deteriorate readily, transfusions of **fresh** blood are given in the immediate pre-operative period to provide some platelets during the operation until the splenic pedicle can be clamped. This removes the spleen from the circulation so that it no longer exerts its effect on the platelets.

Various considerations regarding technique of splenectomy based on physiologic concepts in relation to the specific diseases are presented under splenectomy in general.

In the **post-operative course** the bleeding usually ceases almost immediately. Actually the capillary oozing of the blood from the operative raw surfaces which continues uncontrollably, can be seen dramatically to begin clotting within a few moments after the pedicle of the spleen has been clamped. The platelet level in the perpheral blood afterwards may rise very slowly or rapidly. Usually a level well above normal is encountered in the first few post-operative days, the platelets then decreasing to either normal or to slightly above the preoperative levels. Yet, in these instances of low platelet levels post-operatively, bleeding due to this disease does not ordinarily recur. Another aspect of both the immediate and late post-splenectomy periods is the occasional occurrence of persistent excessively high platelet levels in the peripheral blood associated with episodes of phlebothrombosis and an occasional subsequent embolization. Splenic and portal vein thrombosis are among the most common causes of post-operative deaths following splenectomy in general. The use of anti-coagulants in the presence of excess levels of platelets has been suggested. Other complications are presented under **post-operative complications** as a whole. The important question of overlooked accessory splenic tissue which is not removed at the time of splenectomy is discussed under **accessory spleens.**

Congenital Hemolytic Icterus

Active congenital hemolytic icterus is considered in a patient presenting anemia associated with mild jaundice, a family history of jaundice—particularly of recurrent episodes in members of the family or even in the patient, and an enlarged spleen. The erythrocytes are basically spherocytic, and also microcytic. There is an increased fragility of the red corpuscles to hypotonicity, and a relatively high reticulocyte count in the

peripheral blood. These findings appear logically simple when considered as sequelae to the formation of the spherocytic red corpuscle. The biconcavity of the corpuscle becomes flattened or convex. The surface area of a spherocyte in relation to its total mass renders it more fragile than normally. In serial dilutions of saline, normal red cells begin hemolyzing at a concentration of 0.417 per cent or at 0.45 per cent. A refined technique as devised by Wiseman consists in diluting the patient's own serum with different proportions of water so that the osmotic pressures in each test tube of a series is identical to the similar tubes of a saline dilution series.

The hemolysis occurs prehepatically, the break-down of the hemoglobin to a bilirubin-proteinate occurring primarily in the splenic tissue and possibly in other reticulo-endothelial depots. Jaundice results because the amount of protein-bound bilirubin in the circulation following **excessive** hemolysis is greater than that which the liver can absorb and excrete as protein free bilirubin. Thus the jaundice is mainly of excess serum bilirubin which is protein-bound, and which thus yields an indirect Van den Bergh reaction. The **indirect** Van den Bergh reaction means that addition of alcohol to the serum is required to free the bilirubin from its bound protein first, so the usual color reaction with free bilirubin may be elicited. Because no obstruction in the biliary passage exists usually, an excess of free bilirubin is excreted into the intestinal tract. Oxidation of the bilirubin to urobilinogen by bacterial action occurs in the intestinal tract, and thus the excess of bilirubin gives rise to excess urobilinogen. Although by far most of the urobilinogen is excreted in the feces, some is absorbed by the portal venous system, and, failing to be absorbed by the liver for excretion because of excess quantities, is excreted, instead, by the kidneys. Because of the excess quantities involved, the urine which normally contains a faint trace of urobilinogen now contains 3 to 4 plus quantities.

The enterohepatic circulation of bile pigment—that is, the presumed absorption of free bilirubin and, of course, its oxidized product, urobilinogen, from the intestinal tract into the portal venous system from which they are partially reabsorbed into the hepatic cells and re-excreted through the biliary passages back into the intestinal tract may explain the occasional presence of free bilirubin in the urine, without mechanical biliary tract obstruction. Because the free bilirubin is excessive some of it passes through the liver before there is opportunity for reabsorption of most of it from the portal radicles, and thus some enters the systemic arterial circulation. Free bilirubin in general is excreted through the kidneys if the serum concentration of bilirubin is above its renal threshold of 2 mgm. per cent. However, the intensity of hemolytic jaundice is usually mild as compared to that of mechanical obstructive jaundice.

Further sequelae to the excessive hemolysis is reflected in the relatively high reticulocytosis. Reticulocytosis is indicative of excessive proliferation or regeneration of the red cell series in the marrow. Such regeneration results in delivery of immature red cells (reticulocytes) to the peripheral blood. Characteristically, the highest reticulocyte counts in peripheral blood occur in congenital hemolytic icterus. In one instance over 90 per cent of the red cells in the peripheral blood were reticulocytes in addition to a few normoblasts. This is the evidence of a hypersplenic mechanism—increased marrow regeneration with its resultant peripheral reticulocytosis, balanced negatively by the excessive hemolysis which results in the anemia and jaundice.

An enlarged, palpable spleen is present more or less constantly. During the intense activity of progressive hemolytic anemia, part of the splenic enlargement is due to a process known as sequestration. Sequestration is the removal from the circulation of appreciable numbers of cells into the splenic sinusoids, where they are more or less temporarily stored. The type of cells principally sequestered are those which are principally deficient in the peripheral blood. Evidence of this phenomenon is indicated in part by an adrenalin test. Because of the smooth muscle within the capsule of the spleen, the capsule contracts following intra-

muscular injection of one cubic centimeter of adrenalin. This contraction reduces the size of the spleen, the reduction being usually discernable both by percussion and palpation. A portion of the cellular contents of the spleen are thus forced out into the circulation, and can be measured to some degree by peripheral blood counts which show a markedly proportional rise of those types of cells deficient in the peripheral blood, such as red corpuscles in this instance.

Inasmuch as the large numbers of red cells sequestered into the sinusoids of the spleen remain in contact with the reticulo-endothelial cells, perhaps the time and opportunity for becoming phagocytosed is thus greatly increased when compared to cells rapidly and freely gliding on past the phagocytes, as occurs in an active circulation.

There are indications that the activity of this disease is always present, though most often to a very minor degree, such as a mild reticulocytosis and slightly increased fragility of the erythrocytes. The increased incidence of accessory spleens in this hyperplastic splenic disease is indicative of this. Under various circumstances, the "smouldering" disease becomes quite active, with an anemia and jaundice of varying intensity developing. A fracture or other injury, or an upper respiratory infection, or some other disease may precipitate an intensification of the hemolytic icterus. Therefore, splenectomy, which is the most effective treatment, is always indicated for congenital hemolytic icterus whether the disease be quiescent or active. An important factor, however, is the decision for immediate or emergency splenectomy in the presence of a hemoclastic crisis. When the patient's jaundice is rapidly deepening by the hour and the erythrocyte count decreasing as steadily, it is vital to treat such progressive anemia of congenital hemolytic icterus by emergency splenectomy. Supportive transfusions intended to increase the peripheral red corpuscle count and the hemoglobin prior to splenectomy merely tends to increase the rate and quantity of hemolysis, with resulting deeper jaundice and the more probable occurrence of bile nephrosis, even though normally shaped red cells are given—in addition to prolonging other deleterious effects of this disease.

Approximately seventy-six per cent of cases of congenital hemolytic icterus develop chronic gall bladder disease, the most of which are associated with cholelithiasis of pure pigment. This appears to be due to the excessive pigment which is carried through the biliary tract over a period of years.

Occasionally a pigment stone becomes lodged in the common duct, causing an obstructive jaundice. This complicates the usual congenital hemolytic icterus considerably. Under the circumstances, it is wiser, as experience has shown, to splenectomize before removing the obstructing stones and the gall bladder. Otherwise the surgical procedure of removing the stones first may precipitate a hemoclastic crisis by hemolysis, forcing an emergency splenectomy with intense anemia to be done during the early convalescent days following the choledochotomy. A splenectomy and a choledochotomy at one operative period is not advisable.

Also, in association with the excess bile pigment and chronic cholelithiasis it is not unusual—after the disease has endured for many years—for moderate liver damage to occur as indicated by various liver function tests and as noted grossly at operation or even by biopsy. Therefore, an occasional instance of congenital hemolytic icterus may superficially resemble a Banti's anemia with its concomitant liver damage.

Banti's Syndrome

Splenectomy in the treatment of Banti's syndrome is much less spectacular in its results, particularly because the associated liver damage—if present, and usually is—is not substantially improved if at all, as is also true of any associated portal hypertension. Furthermore, the surgery is more hazardous because of hemorrhages due to deficient prothrombin (result of liver damage) or due to splenic thrombocytopenia, and also because of frequent adhesions of the spleen to surrounding structures. Yet, an instance of hypersplenism in one with

Banti's syndrome is an indication for splenectomy, and the splenectomy usually results in alleviation of this malfunctioning state. Even the hemorrhage from esophageal varices of portal hypertension have occasionally been associated with a thrombocytopenia presumably of hypersplenic type. An anemia, splenomegaly, and a leukopenia with a normal differential may cast suspicion of a Banti's syndrome. Evidence of associated portal hypertension, such as dilated thoracoepigastric veins, a caput medusa, and esophageal varices in the presence of hypersplenic peripheral blood deficiencies further supports a diagnosis of Banti's syndrome. Perhaps it may at times be difficult to differentiate a Banti's anemia, with its frequent liver damage, from a true liver cirrhosis. Furthermore, Banti's syndrome as such, is gradually becoming a less encompassing disease inasmuch as several different specific disease entities have been separated out from this general disease pattern, such as primary splenic neutropenia and pansplenic hematocytopenia.

Primary Splenic Neutropenia and Pansplenic Hematocytopenia

The original descriptions and establishment of two primary hypersplenic diseases by Doan and Wiseman have been designated by them as primary splenic neutropenia and pansplenic hematocytopenia. In primary splenic neutropenia the hypersplenism affects only the neutrophils. Thus, the patient presents a clinical picture partially similar to the well-known agranulocytic angina, and perhaps other clinical manifestations of lowered resistance to infection, associated with a peripheral leukopenia (neutropenia), a moderate splenomegaly, but without a deficiency if not actually a hyperplasia of neutrophilic myelocytes in the marrow. Splenectomy has proven to be very effective in eliminating this neutropenia and its consequences.

In pansplenic hematocytopenia the hypersplenism affects all cellular types of the peripheral blood and thus there is presented an anemia combined with a leukopenia, and a thrombocytopenia and associated with a moderate splenomegaly. The marrow presents a hyperplasia of the precursor cells of all the cell types. Splenectomy in this disease is similarly effective in restoring the peripheral blood picture to normal levels.

Secondary Hypersplenism

Secondary hypersplenism may perhaps be approached with only mild enthusiasm inasmuch as a splenectomy obviously does not eliminate a fundamental disease such as leukemia, Hodgkin's disease, Gaucher's disease, an infectious granuloma (tuberculosis, moniliasis, etc.), or lymphosarcoma. However, not too infrequently Hodgkin's disease, for example, is ushered in clinically with manifestations of hypersplenic thrombocytopenic hemorrhages, or, a lymphatic leukemia is complicated by hemorrhages of a similar etiology or by a hemolytic icterus. And, the same complications may occur in Gaucher's disease or with a tuberculous spleen. Splenectomy apparently will appreciably prolong the lives of such patients usually by alleviating the hypersplenic thrombocytopenic hemorrhages or the hemolytic anemia and the jaundice or the hypersplenic leukopenia. Because of the associated pathologies in the secondary hypersplenisms, the myelophthisic deficiencies must be carefully differentiated from hypersplenism from both diagnostic and therapeutic aspects. Not infrequently a thrombocytopenia or an anemia or a leukopenia when associated with a leukemia or lymphosarcoma or a Gaucher's disease is the result of replacing the normal proliferative elements of the marrow by the particular pathologic cells. Thus in such diseases a myelophthisic anemia, a myelophthisic thrombocytopenia or a myelophthisic leukopenia may occur. Splenectomy has no appreciably favorable effect upon myelophthisic deficiencies, and in the thrombocytopenic type definitely aggravates the already existent pre-operative hemorrhages by bleeding from all the wound edges both in the incision and intraabdominally.

Technique of Splenectomy

Anesthesia for splenectomy should attempt to supply the maximum amount of oxygen because of the usually intense

grades of anemia, and also avoid marked dilatation of the spleen. Cyclopropane permits the highest percentages of oxygen. Barbiturates and ether tend to dilate the spleen.

A technique of splenectomy seemingly adequate for almost any spleen utilizes a relatively long left upper paramedian abdominal incision. Thereafter the technique varies with the type of hematologic dyscrasia and anatomical factors such as the size of the spleen, the presence or absence of adhesions to the spleen, the length of the splenic pedicle (particularly the lieno-renal ligament) and whether or not manipulation with its concomitant contraction of the spleen is physiological ly deleterious or whether it is beneficial.

The size of the spleen being normal in primary thrombocytopenic purpura and it being deleterious to manipulate the spleen because its presumable pathic hormonal content is thus extruded into the circulation, exposure of the spleen and the clamping of its pedicle without manipulating or dislocating the spleen from its site is indicated, but perhaps may be somewhat difficult. Exposure of the splenic area may be obtained by: 1) the second assistant with broad retractor in the incisional wound, retracting the left costal margin upwards and outwards, and 2) by the third assistant retracting with a sponge the greater curvature of the stomach medially. The splenic pedicle is next clamped with the spleen in situ if possible. This maneuver thus involves the least manipulation of the spleen.

If the splenic pedicle cannot be safely clamped with the spleen in situ, the alternative procedure is to deliver or dislocate the spleen up into the wound—if that can be done. Whether the spleen can be dislocated safely and readily up into the wound depends in part upon the length of the spleno-renal ligament (the posterior leaf of the splenic pedicle). First, the spleen must be freed of adhesions. In this disease (primary thrombocytopenic purpura), however, adhesions to the spleen very rarely occur.

If the lieno-renal ligament be of sufficient length to dislocate the spleen upwards it is safest to do so with the right hand while the pedicle itself is held firmly from above between the thumb and the fingers of the left hand. The firm grip of the left hand on the pedicle is intended for safety in the event that an arteriosclerotic splenic artery breaks because of angulation when the spleen is brought up. This has occurred, and exsanguination was avoided merely by compression of the vessels already in hand—a most expedient safety measure. On the other hand, most of the patients with primary thrombocytopenic purpura are relatively young and thus do not usually present arteriosclerosis of the splenic artery.

Once the spleen is brought up into the wound, the space previously occupied by the spleen is filled with large laparotomy packs so that the spleen cannot fall back. The spleen is steadied by the first assistant with the least possible pressure being exerted upon it, thus avoiding a substantial compression of it.

Whether the spleen be exposed for its removal in situ or it be dislocated up into the abdominal incision wound, the next procedure is to clamp, sever and ligate the pedicle. Modified hysterectomy clamps, modified by being curved along their entire length so that the convex side fits up against the concave hilus of the spleen, and so that the concavity of the clamps fit well up against the greater curvature, without at the same time clamping stomach or splenic tissue, are advantageously used. Three such clamps are closely applied around the splenic pedicle, including within them both the gastroplenic omentum and the lienorenal ligament. The splenic pedicle is severed between the two clamps nearest the spleen, and thus splenectomy is accomplished. Two heavy ligatures are placed, No. 3 catgut or heavy braided silk, one in each groove made by the previously applied forceps, as each is removed, in addition to the third ligature which is placed proximally.

This procedure admittedly does not separately ligate the splenic artery and vein, as may sometimes be done. However, it should be realized that there are two types of splenic artery, the magistral and the distributed type. The magistral

type is the long, single channel type which does not divide until reaching the immediate hilus of the spleen. This type could easily be ligated from its posterior aspect, or even from an anterior approach if the gastrosplenic omentum is first opened. However, if the splenic artery is of the distributed type, i.e., one which divides into several branches at a relatively long distance from the hilus of the spleen, then the several branches of the splenic artery rather than a single vessel must be ligated and severed, and it thus may become a more time consuming and more complex procedure. Also, by ligating the vessels separately the lesser omental bursa is incidentally opened. The lesser omental bursa must then be subsequently closed so as to prevent an internal hernia. Also, in the event of an incorrect diagnosis in a patient with hemorrhages, the bleeding which occurred preoperatively continues postoperatively in addition to bleeding from all the cut surfaces incident to the operation. There is much less chance of exsanguination if a series of ligatures encompasses the entire pedicle and all of its vessels en masse. In a specific instance of a pseudohemophiliac coming to splenectomy by error, this undoubtedly was life-saving, inasmuch as the incisional bleeding was eventually controlled after a few days by constant pressure onto the wound. Had there been separation of tissue for individual vessel ligation, internally, at the pedicle, the child would most probably have bled to death, inasmuch as manual pressure from outside of the abdomen obviously could not have been applied to the splenic vessels. Because the ligatures are thus applied around the entire pedicle, dilatation of the stomach would tend to displace the ligatures even with a needle ligature. Therefore, postoperative distension of the stomach is studiously avoided by continuous gastric suction for the first 48 hours.

A most dramatic physiologic phenomenon is observed following splenectomy for primary thrombocytopenic purpura. Whereas during the incision there is uncontrollable capillary oozing throughout the incision and from every cut surface within the abdominal cavity, yet seemingly within 60 seconds after the spleen has been removed from the circulation by the clamping of its pedicle, clots begin to form and the bleeding is controlled.

Occasionally bleeding persists for several hours after splenectomy. Since the spleen in primary thrombocytopenic purpura is presumed to contain a humoral factor to account for its effect on platelets, its normal size being consistent with a humoral mechanism, manipulation of the spleen with its consequent compression and expulsion of this bleeding or thrombocytopenic factor into the circulation might be responsible for the delayed inhibitory effect upon the bleeding. Hence, manipulation and compression of the spleen in splenic thrombocytopenic purpura is studiously avoided.

Following removal of the major spleen, accessory spleens are sought, and if present removed.

Splenectomy for congenital hemolytic icterus presents several differences from splenectomy for primary thrombocytopenic purpura. First, the patient is hemolyzing blood excessively and is quite anemic. Experience has shown that deepening of the jaundice occurs following transfusion—even of normally shaped red cells. Thus, to possibly prevent greater amounts of bile pigment from flowing through the kidneys, which thus is more apt to block the tubules with bile casts and cause bile nephrosis, no preoperative blood is given. However, because of the gravity of the anemia, the blood is readied. With an intravenous saline drip in place, administration of the blood is begun during the operation the moment the splenic pedicle is clamped.

Because the process of hemolysis apparently occurs **within** the structure of the spleen there is no fear of prolonging or intensifying the hemolytic process by manipulation and compression of the spleen. Furthermore, the spleen is enlarged in this disease and contains considerable amounts of blood as a result of sequestration. It is advantageous to reduce the size of the spleen. This materially aids in the process of removing the spleen, as it is easier to dislocate a

smaller-sized spleen (though still larger than normal) up into the wound, and this procedure also adds a considerable number of erythrocytes to the highly anemic circulation (an auto-transfusion). Reduction in size of the spleen is brought about in two ways—(1) by massaging the spleen, which stimulates the smooth muscle of the splenic capsule, and (2) by the purposely forced manual compression of the spleen by the surgeon's hands. The spleen is then delivered into the wound in the manner previously described—if possible, and the pedicle is clamped completely across its width with the three specially curved long hemostats. If vessels are individually clamped and ligated it is important to clamp the arteries before the veins, as the reverse procedure would result in a rapid and considerable accumulation of blood within the spleen.

Accessory Spleens

To help prevent recurrence of congenital hemolytic icterus or of primary thrombocytopenic purpura, it is apparently essential to find and remove all accessory spleens which may be present. This is done after the major spleen has been removed and complete hemotasis obtained. Accessory spleens are found relatively frequently, particularly in those with congenital hemolytic icterus and to a less extent in those with primary thrombopenic purpura. Also, they are more frequent in the younger patients than in the older patients. In those without splenic disease the incidence of accessory spleens also decreases with advancing age, but the incidence in general is less than in those with splenic disease. Also, accessory spleens occur less frequently in primary thrombocytopenic purpura than in congenital hemolytic icterus, and this might be expected inasmuch as splenic hyperplasis does not occur in primary thrombocytopenic purpura (normal sized spleen). The explanation for the normally decreasing incidence of accessory spleens coincident with advancing age is that as the major spleen begins to involute from the time of birth onwards and since the accessory splenic tissue partakes of the same processes, so would an accessory begin to do so. Because the accessory is markedly smaller it might very readily completely atrophy eventually thus leaving fewer accessory spleens intact with the passing of years. An example of the incidence of accessory spleens in the different diseases and in different age groups may be cited from the Curtis and Movitz series. In congenital hemolytic icterus, 57 per cent of the patients in the first decade presented accessory spleens, 43 per cent in the second decade, and 13 and 14 per cent in the third and fourth decades. In primary thrombocytopenic purpura, 44 per cent of the patients in the first decade presented accessories, 33 per cent in the second decade, 37 per cent in the third decade, none in the fourth, and one patient in the fifth decade. The incidence among children with splenic disease is lower.

The locations of the accessory spleens and their usual incidence in each of these locations are as follows: (Fig 1.) hilus of spleen, 54 per cent; splenic pedicle, 25 per cent; great omentum, 12 per cent; retroperitoneal area surrounding tail of the pancreas, 6 per cent; splenocolic ligament, 1.5 per cent; and bowel mesentery, 0.75 per cent. Other locations which present accessory spleens though with less frequency are in the body and tail of the pancreas, and in the scrotum attached to the left tunica albuginea in the male. Because of the embryonic relationship of the mesovarium of the female to the tunica albuginea of the male, it is advisable to explore the left mesovarium. To date none have been reported as attached to the ovary. Other rare locations will be referred to presently. The number of accessory spleens in any one location may vary from 1 to 8, and it appears that approximately 10 is the largest number found in any one patient.

A further survey of the distribution of accessory spleens reveals that in 85 per cent they are found in a single location. That is, from 1 to 8 accessories are found at the splenic hilus or on the pedicle, or attached to the great omentum, etc. In the remaining 15 per cent of patients with accessory spleens they

are present in two different locations. Apparently they almost never occur in more than two locations. Furthermore, it appears that when present in two locations, that the hilus is always one of the two locations. Thus, the pattern of distribution of accessory spleens is helpful in determining whether one's search for accessory spleens is completed. For example, since the hilar accessories are quite obvious both during the process of splenectomy and immediately upon removal of the spleen, in the event that accessory spleens have been found in one other location other than at the hilus, the surgeon may thus realize that all the accessories have been found. The absence of accessory spleens at the hilus does not, of course, preclude the possibility of accessory spleens in any one of the previously indicated locations. But having found one or more in any one location except the hilus, one is reasonably certain that no others exist except those which are at the obvious splenic hilus.

It is interesting to note that in each of the several reported cases of overlooked accessory spleens that were later found, all except one were located retroperitoneally in the area surrounding the tail of the pancreas. The exception was retroperitoneally also, but along the course of embryonic descent of the left testis, inferior to the kidney.[5]

The recurrence of congenital hemolytic icterus or of primary thrombocytopenic purpura attributable to an overlooked accessory spleen is characterized usually by a varying period of remission from the disease (2 to 4 years) following the splenectomy. Thus, a patient with hemorrhage from primary thrombopenic purpura will usually stop bleeding soon after the removal of the major spleen although accessory spleens may have been overlooked. Similarly, a patient with congenital hemolytic icterus will stop hemolyzing excessively following removal of the major spleen, even though accessory spleens have been overlooked and are still present within the patient. These accessory spleens may cause recurrence subsequently, but usually do not do so in the early post-operative period.

The accessory spleens, however, are not looked upon by all as the entire answer to the problem of recurrence of either of these two diseases following splenectomy because in some instances of recurrence no accessory spleens were found. However, one is more prone to accept positive evidence rather than negative evidence. For instance, the recurrence of primary thrombopenic purpura in the patient whose abdominal cavity revealed no accessory spleens on thorough search at the time of re-exploration would tend to discredit the accessory spleen relationship to recurrence. However, upon searching along the retroperitoneal route of embryonic descent of the left gonad, an accessory spleen was found, and following its surgical removal the patient recovered from the recurrence as spectacularly as following the major splenectomy.[5] Similarly, the instance of recurrence of congenital hemolytic icterus four years after splenectomy which promptly recovered following an accessory splenectomy is positive evidence. Furthermore, it is difficult to explore the substance of the pancreas in vivo where some accessory spleens are known to occur. Also, embryologically there is reason to presume the possibility that accessories may be present in the posterior mediastinum adjacent to the esophagus, inasmuch as the esophagus is embryonically suspended by the same dorsal mesogastrium upon which the development of the spleen occurs.

The occurrence of an accessory spleen in the scrotum may be traced embryologically to the fact that originally the genital ridge from which the gonad develops overlies the mesonephros and is immediately adjacent to the embryonic spleen. The spleen embryonically is formed by fusion of separate splenic hillocks arising on the left side of the dorsal mesogatsrium just dorsal to the stomach. Accessory spleens appear to arise because of failure of fusion of one or more of these separate splenic hillocks. Their eventual locations at various distances from the major spleen is apparently the result of the formation and development of the dorsal mesogastrium subjacent to the splenic hillocks into the various peritoneal ligaments and bursae,

which thus carry the accessory spleens along with them. Further evidence of this mode of accessory spleen formation is noted in the development of the splenic artery and its branches, which provide a similar blood supply to both splenic lobule and acessory spleen, i.e., one branch supplying a portion of spleen and the other branch an accessory spleen. Also, the spleen with several notches is more likely to be associated with accessory spleens than the spleen with but one or no notch. The notch represents incomplete fusion, or a tendency towards failure of fusion of the splenic hillocks. And, the splenic artery which divides into several branches at a distance from the spleen before reaching the hilus (the distributed type) rather than being a straight single vessel, is more likely to be associated with a notched spleen and supply an accessory spleen. Thus, an embryonic splenic hillock which fails to fuse with the major spleen may become attached to the developing gonad (i.e., its mesentery) and descend with it into the left scrotum or into the left pelvis.

Besides overlooked accessory spleens as a factor in recurrence, there is the possibility of **splenosis** being a factor. Splenosis is quite different from accessory spleens. **Splenosis** consists of small splenotic nodules found throughout the peritoneal cavity, varying in number from 42 to 400, situated on various serosal surfaces as well as on the parietal peritoneum and lesser omentum. Whereas, true accessory spleens are developed embryonically and hence are located on those peritoneal surfaces derived from the dorsal mesogastrium, never occurring on the parietal peritoneum or on the lesser omentum or in the head of the pancreas, splenotic nodules of splenosis arise by growth of bits of splenic tissue implanted widely throughout the peritoneal surfaces by the blood issuing forth from a ruptured or torn spleen. Splenosis is the usual finding in those patients recovering from a splenectomy for a ruptured spleen. Subsequent confirmation of the occurrence of splenosis following recovery from splenectomy for a ruptured spleen is usually made at necropsy, or at laparotomy done for (1) intestinal obstruction (most frequent complication or splenosis) or for (2) an intercurrent surgical disease such as acute appendicitis, or for (3) misdiagnosed pelvic complaints resulting from the pelvic location of splenotic nodules, even being mistaken grossly for endometriosis.

Splenosis assumes importance in relation to the usual splenectomy because of accidental tearing or cutting into or puncturing the spleen during the splenectomy. Spillage of splenic tissue fragments onto the peritoneal surfaces or even into the incisional wound may thus occur, and it is reasonable to assume that the resulting splenotic nodules might function in a pathologic manner similar to that for which the major spleen was removed. Experimentally, splenic fragments are easily implanted onto and grow in muscle tissue or in subcutaneous fat—showing also the importance of a protective covering of the incisional wound during a splenectomy. Interestingly, one case report of recurrence of congenital hemolytic icterus which came to necropsy indicated that all the "hemolymph" nodes throughout the abdominal cavity were enlarged and were considered responsible for the recurrence.[4] Inasmuch as hemolymph nodes are limited in the abdomen to the peri-aortic position and are few in number, and whereas hemolymph nodes may be confused with splenotic nodules his-

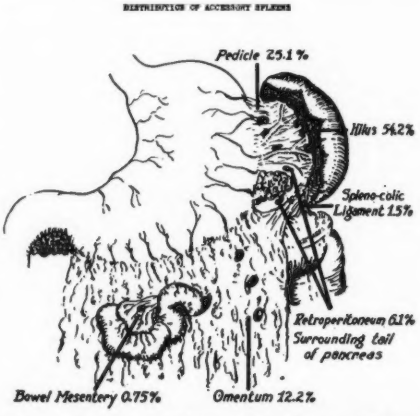

Fig. 1. Location incidence of Accessory Spleens.

tologically, and whereas splenotic nodules rather than hemolymph nodes are found widely distributed in the peritoneal cavity, and since splenosis has been shown to consistently follow after an interval of time the occurrence of torn spleens, it is reasonable to reinterpret this recurrence as possibly due to splenosis rather than to hemolymph nodes. Since the proposal of this concept in 1946 one case as such has been reported by Stobie[4] which indicated the recurrence of congenital hemolytic icterus as due to splenosis resulting from a torn spleen incident to a difficult splenectomy. Stobie's case report definitely shows that splenosis may occur following the usual splenectomy but the recurrence of congenital hemolytic icterus is not certain.

Recurrences have been postulated also as due to compensatory function of the reticulo-endothelial system in general.

Whether accessory spleens bear an etiologic relationship to recurrence of primary splenic neutropenia or pansplenic hemotocytopenia cannot be told as yet. But, the patient undergoing splenectomy for such diseases as well as for any of the secondary hypersplenisms, should have all accessory spleens removed at the same time, and care should be exercised to prevent possible splenosis as well.

Complications of Splenectomy

The mortality rate in splendectomy in general in large series of cases in the most experienced hands averages about ten per cent, but recently there has been some improvement, particularly in those centers keenly aware of the physiologic and emergency aspects of congenital hemolytic icterus and primary thrombocytopenic purpura, as well as the inherent dangers of splenectomy for Banti's syndrome. The three most important post-operative complications of splenectomy are: (1) hemorrhage, (2) portal vein thrombosis, and (3) liver damage.

Hemorrhage may be due to (a) technical errors or difficulties resulting in bleeding from the pedicle or from adhesions to the spleen which may be traversed by vessels, or (b) continuation of the hemorrhage due to the disease for which splenectomy was done, or (c) to prothrombin deficiency which occurs with liver damage.

Thrombosis following splenectomy accounts for 29 per cent of the deaths in the largest reported series of splenectomies. A probable factor for the relatively high incidence of post-operative thrombosis peculiar to splenectomy is the post-operative rise in blood platelets. Even patients splenectomized for deficiencies of platelets may occasionally present persistent excessively high levels of platelets, such as 2 million per cubic millimeter. This was observed in a patient with primary thrombocytopenic purpura following splenectomy and was associated with repeated episodes of thrombosis in the lower extremities and a non-fatal pulmonary embolization.

Post-splenectomy high blood platelet levels occur more frequently, however, in those instances without pre-operative deficiencies of platelets. For example, in Banti's syndrome, some patients whose platelet levels are normal may be expected to experience a post-operative rise above normal levels whereas those patients whose hypersplenism affects the platelets to a minor extent with the platelets being low will usually exhibit a post-splenectomy rise in platelets to approximately normal levels. A similar response is noted usually in congenital hemolytic icterus. It has been suggested that those patients showing high post-operative platelet levels be given prophylactic anti-coagulant therapy.

Liver deaths occur with varying frequency post-operatively in different reported series. These are particularly prominent because of the frequently associated liver damage, particularly in Banti's syndrome and occasionally in congenital hemolytic icterus.

Contra-indications to Splenectomy

Splenectomy is contra-indicated in peripheral blood deficiencies (cellular) without coexistent hypersplenism. Also, experience indicates that patients with myelogenous leukemia do not do as well with a splenectomy. Polycythemia vera is a contra-indication.

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COR PULMONALE: A SEQUEL TO CHEST DEFORMITY

GEORGE LEWIS, M.D.

Discussant: Peter Gaberman, M.D.*

Primary cor pulmonale is a cardiac disorder arising from a lesion located between the mitral valve on the left and the mouths of the vena cavae on the right.[1] It does not include those cardiopathies in which both right and left heart failure occur simultaneously. Brill[1] includes mitral stenosis as a cause of cor pulmonale, but others do not. Secondary cor pulmonale is a consequence of antecedent left heart failure. Primary pulmonary heart disease will be considered here.

This condition is divided into acute, subacute, and chronic types.[2] The acute form is embolic in origin and usually massive; if 60 per cent of the pulmonary vascular bed is occluded, death will occur almost immediately. Numerous small emboli blocking many of the smaller branches of the pulmonary artery will produce the same effect. It also is a cause of the second type, the subacute form. While this group is the least frequent, the most common cause is metastatic endolymphatic carcinomatosis, the primary site being in the stomach, breast, prostate, liver, kidney, or the lung itself. The metastasis invades the perivascular lymphatics and the arterioles of the lung blocking them and producing intimal proliferation within these vessels. This carcinomatous lymphangitis and endarteritis interferes with the blood flow through the lesser circulation and throws a burden on the right ventricle with eventual failure. The third type, chronic cor pulmonale, may arise from changes in bony structures of the chest, the pulmonary vascular tree, or in the lung parenchyma. Cor pulmonale produced by thoracic deformity is the subject of discussion here.

Hill[3] states that pulmonocardiac failure from chest deformity is not rare and that the incidence of scoliosis in children following acute anterior poliomyelitis is 5 to 30 per cent. The deformity usually begins within five years after the acute illness and progresses during the growth period. Scott and Garvin[4] studied 50 autopsied cases of cor pulmonale and found one case secondary to kyphoscoliosis. Spain and Handler[2] reported on cases of deformity in the 60 cases they observed. Surgically produced chest deformities may cause cor pulmonale and pulmonocardiac failure. Thoracoplasty for pulmonary tuberculosis is another cause.[2]

The pathology in these cases is similar.[3] The bony structural change usually is obvious and may consist of kyphosis, kyphoscoliosis, pigeon-breast, or any combination of these. The pulmonary findings reveal small lungs which even may resemble a child's. Atelectasis, emphysema, and pneumonias of varying extent may be seen. The diaphragm is high. The cardiac changes consist of hypertrophy of the right ventricle over the upper limit of the normal 0.5 cm. Dilatation is present. The right auricle may

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be dilated and the pulmonary artery is widened. The left ventricle may be hypertrophied, but not to the degree that is seen in the right heart. This enlargement of the left heart can be found with no clinical or pathological evidence of hypertension, coronary artery disease or valvular disturbances. The cause will be discussed later. All the viscera reveal marked passive congestion. Ascites and other effusions are present. The general development of the body usually is retarded.

The clinical picture results from anoxia and right heart failure.[1, 2, 3; 6] Cyanosis, habitual dyspnea, clubbing, fainting, giddiness, and mental symptoms are ascribed to anoxia. The patient is able to lie flat and has no orthopnea unless left heart failure has occurred or there is secondary infection with bronchospasm.

Strain and failure of the right cardiac chambers produce increased venous pressure accounting for the engorged superficial veins, subcutaneous edema, visceral congestion, effusions, oliguria with albuminuria and hematuria. The second pulmonic sound is accentuated, but murmurs are rare. There is a tachycardia and a gallop rhythm, but arrhythmias are unusual. McMichael[7] points out that when the heart fails, the nose, ears, and hands are warm, indicating a high output failure. Hypertrophy and dilatation of the right side of the heart is revealed by the enlargement of the outflow tract of the right ventricle on roentgen examination. The diastolic blood pressure is elevated, but the systolic level is increased only slightly.[6] The electrocardiogram shows a right axis shift or a right heart strain pattern. Terminally, there is general cardiac failure.

The diagnosis of pulmonocardiac failure does not become obvious until the signs of passive congestion appear, but a presumptive diagnosis can be made when the dyspnea and cyanosis increase.

The course is rapidly downhill and the patient usually is unable to live through two episodes of failure, as the right ventricle is not capable of adapting to the increased work placed on it by the increased resistance in the lesser circulation.[7] The average age at death of these patients is 30 years and these patients are prone to sudden death.[6]

Prevention of the thoracic deformity or early correction is the best prophylaxis against cor pulmonale.[3] However, if pulmonary heart disease develops, it is imperative to prevent infections of the respiratory tree, as these further embarrass the ventilation by reducing the vital capacity and aggravating the strain on the right heart.[6]

Active therapy of pulmonocardiac failure evolves about oxygen, bronchodilators, antibiotics, keeping the air passages free from secretion and **no** morphine. Digitalis and venesection are contraindicated according to McMichael and his co-workers.[7] He classes pulmonary heart disease failure as a high output failure; that is, the cardiac output is increased and the venous pressure is a compensatory mechanism to assist the filling of the heart to maintain this output. Digitalis and venesection produce a fall in venous pressure and thus reduce the cardiac output which is necessary, although inadequate. He stresses the administration of oxygen, as the oxygen saturation of the arterial blood may be as low as 50 per cent.

In considering the pathological physiology, several problems arise. Of primary concern is the mechanism by which cor pulmonale is produced in structural changes of the chest. These changes produce a small thorax with a high diaphragm. The excursions of the ribs are limited by the distortion of the resting position which results in poor effective mechanical movement during inspiration and expiration. The lungs are small and show atelectasis and emphysema. Whereas the normal ratio of residual air to vital capacity is 0.6, in chest deformities it is 1.3. The ratio is increased because the vital capacity is reduced by the above changes. The reduced thoracic volume, poor respiratory movement, and reduced vital capacity lessens the respiratory volume considerably and, as a consequence, there is inadequate ventilation with low oxygen and high carbon dioxide concentrations in the pulmonary tree. This elicits in-

creased respiratory effort to overcome the mechanical handicaps and to maintain gaseous exchange. Hence, an explanation for the habitual dyspnea. Despite the increased work, less oxygen is removed from the inspired air and the low oxygen and high carbon dioxide concentration persists.[3, 6]

If an animal[8] or man[7] breaths a low oxygen concentration (10 to 11 per cent oxygen in nitrogen) the pulmonary arterial pressure is found to increase. This increase is not influenced by vagotomy or extirpation of the stellate ganglia. Although this does not rule out a reflex of unknown nature, the response is thought to be a local one within the vessels themselves. A high carbon dioxide concentration will produce a similar effect. Breathing pure oxygen causes a fall in pulmonary arterial pressure. In the systemic circulation, such a carbon dioxide concentration produces a vasodilatation, but in the lesser circulation, vasoconstriction occurs acting as a peripheral resistance to the right ventricle. This will cause the pulmonary arterial pressure to rise.

In a deformed chest with reduced vital capacity and limited respiratory excursions, poor ventilation results in low oxygen concentration and high carbon dioxide concentration in the respiratory tree. This will produce a vasoconstriction in the pulmonary circuit and raise the pulmonary arterial and right ventricular pressures. The persistent vasoconstriction leads to hypertrophy, dilatation, and later, failure of the right heart.

Why is the left ventricle enlarged? Anoxemia may be the cause. It has been shown that low oxygen concentration to the myocardium is a cause for cardiac hypertrophy.[9] Also, the high output of the heart produces increased work on the ventricle, which is another cause for hypertrophy.[10] However, this increased work increases the demand for oxygen and the functional coronary insufficiency is increased until finally failure occurs in the mal-oxygenated heart. The failure may be sudden, due to pulmonary edema producing death almost immediately. Although digitalis acts to reduce the venous pressure,[7] the latter may rise even while cause of increasing pulmonocardiac failure. The elevated diastolic blood pressure could be related to the tachycardia[9] and perhaps the high output may be a the patient is on the drug therapy befactor.

Morphine is contra-indicated in cases of pulmonary heart disease. In these cases, the depth of respiration is maximal and fixed with poor ventilation. Morphine lowers the respiratory rate and will increase the anoxia and may cause death.[11]

SUMMARY:

Diseases or surgical procedures involving the bony structures of the thorax may produce cor pulmonale. The altered respiratory mechanics results in poor ventilation leading to low oxygen and high carbon dioxide concentrations in the pulmonary tree. Pulmonary vasoconstriction occurs increasing the pulmonary arterial pressure and the persistence of this condition leads to strain on the right heart with eventual failure. The left ventricle is affected secondarily.

The course is rapid and sudden death may occur. Early correction of the deformity is essential to prevent the disease. In the presence of cor pulmonale, therapy is directed to prevent further increases in the strain of the right heart. Digitalis and venesection are contra-indicated in pulmonocardiac failure while oxygen is of prime importance. Morphine will cause death in these patients.

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Discussion

Dr. Gaberman:

The treatment of the heart failure connected with chronic cor pulmonale has been of special interest to us in the medical wards at Cook County Hospital. It has been taught generally and previously that, given heart failure, digitalis was indicated and was of value. However, in 1947 McMichael and Sharpey-Schaeffer in their study on venomotor mechanisms determined that digitalis has a vasodepressor action. Inasmuch as increase of venous pressure is deemed necessary in chronic cor pulmonale to fill the ventricle during diastole against increased pressure, a decreased venous pressure was considered harmful by these two men. For the same reason, phlebotomy was contra-indicated. This seemed to add experimental proof to empirical observation that digitalis was of no great value in isolated right heart failure. On this assumption, in our wards digitalis was discontinued in chronic cor pulmonale. The residents in the wards, who were in more intimate contact with the patients than we were, insisted that the patient without digitalis got along not only as well as, but even better than those who had been given digitalis, and from our observation there we felt the same way.

However, it has come to my attention that McMichael has changed his mind on further experimentation about the disadvantages of digitalis, and now feels that it should be used.

As you can see, the question is still undecided and only time and further experience will guide us correctly. At the present time, I feel that digitalis should be used in these cases unless, in any particular case, we find that it has disadvantages. When it is used, it should be used in full digitalizing doses.

MEDICINE IN ISRAEL *

(Prewar-Military-Postwar)

EMANUEL MARCUS, M.D., Ph.D.**

Introduction

The medical problems in Israel are only a part of an apparently bottomless barrel of problems—social, political, economic—that the people of the world's newest democracy have shouldered. I am sure that the interests of this group are not only in the special interest of medicine, but in all problems of a people fighting for a basic right of humankind—the right to live peacefully without prejudice, to religious origin, and without being prey to the whims of genocidal fanatics—twentieth century style. Accordingly, we shall here assume the liberty of deviating a bit from the announced subject to give you a birds' eye view of Irsael's fight for independence—now a permanent recorded part of the romance of a people.

* Abstract of Seminar delivered at The Chicago Medical School on July 20, 1949.

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General Plan of Medicine Prior to the War

Since the end of World War I, when for practical purposes immigration to Palestine began, there have been three main systems of medical care. The oldest and largest of these is that belonging to and operated by the Histadruth, the federation of labor unions. It is known as the Kupat Cholim (literal translation—Sick Fund), and is essentially a system of pre-payment insurance. The Kopat Cholim operates hospitals and clinics throughout the land, the main institution being the Beilinson Hospital at Petach Tikvah—a first class hospital by any standard. The second system of medicine, both with respect to length of service and size is the Hadassah organization, basically controlled and supported by the women of American Hadassah. In addition to the Rothchild University Hospital in Jerusalem there are Hadassah installations in Tel Aviv, Haifa, Safad (for tuberculosis) and in smaller communities. The third system of practitioners are those engaged in the private practice of medicine and associated with private hospitals. They are by far in the minority. This, for two reasons; firstly, not many people percentagewise can afford private care; secondly, the largest element in the country are there because they are part and parcel of the labor Zionist movement, and they believe in socialized medicine. Large private practices can be counted on the fingers of one hand.

Medicine During the War

When war came to Israel simultaneously with her first breath of statehood, she was as ill-prepared to care for her wounded as she was to wage physical warfare. Until the military medical services could be established the existing medical facilities in the land had to bear the increased load. Wounded men received only minimal first aid until by laborious and hazardous travel they were returned to Kupat Cholim and Hadassah installations. In the early days of the war there was not one senior surgeon who could be released from one of these hospitals to set up a surgical military hospital.

Immediately upon my arrival in Israel early in June, 1948, the Surgeon General asked me to go to the Negev and set up a surgical service for that part of the land. The Negev constitutes two-thirds of Israel by territory as delineated by the United Nations on 29 November 1947. Althought twenty-six first aid stations were already in existence there, mine was to be the first and only hospital with an operating room. My assistant and I went down to the Negev in the last convoy successfully to pass the Kharatiyah crossroad on the Magdal-Faludja line blocked by Egyptian guns and United Nations impotence; in order to pass I drove an armored truck. The military and medical headquarters of the Negev were in the settlement of Ruhama. There three buildings had been set aside for the Hospital, but within the short space of twelve hours it was obvious that the bombing and strafing made any facilities above ground too precarious to run a hospital. Under cover of darkness we moved to an underground series of rooms that had been prepared for me—wards, operating room, kitchen—all eight feet under the ground. Here I was to watch the flow of blood, sweat and tears of a gallant youth, not alone native Palestinians, but friendly visitors of principle, who backed their beliefs and hopes with everything they had to give. On my operating table have been the sons of England, Finland, Irelan, Canada, United States, Australia, South Africa, France, Turkey, Italy, Spain, Belgium and all those of Central Europe who came to settle.

The Negev battle was fought by the Palmach—striking or commando force. The Palmach were front line troops from the very beginning because these nine thousand men were the only trained unit at the outbreak of hostilities; their leader and trainer was a rough and tumble man of sixty-nine years. In June and July the facilities for transporting wounded to my hospital were pitiable. At no time were there enough jeeps and ambulances; not all of those that succeeded in leaving the field of battle reached the hospital—many were attacked and the men again wounded or killed. These conditions obtained because there were no lines in the Negev—everyone was behind everyone else's line. Patients arrived anywhere from twelve to sixty hours after

having sustained serious wounds. The operating team worked constantly on the ever increasing numbers of wounded of all kinds. We were bombed and strafed relentlessly as many as twenty-eight times a day; our defensive weapons were little more than child's play. Our water supply was hit—precluding shaving and showering. The generator was hit—forcing me to work by kerosene lamp and hand-neon lights. At one time we operated for ninety-six hours, stepping back only to change patients. Our entire team was brought to the point of virtual physical and mental exhaustion. At any given time there numbered amongst my patients awaiting evacuation head wounds, neck wounds with pharyngostomy and/or tracheostomy wounds, chest cases, postoperative gastro-intestinal resections, colostomies, arm and leg amputees, cases with casts, injuries to major blood vessels—everything that steel can inflict on flesh. During the extreme heat of the battle it became impossible to evacuate postoperative cases to Tel Aviv. At one time we had thirty patients more than we had beds (the boards that we called beds did not deserve the dignity of the name); that meant that thirty men who had already been wounded had to lay above the hospital on the ground subject to the strafing of the enemy Spitfires. This situation plus the fact that our control of the roads had dwindled led to the establishments of the Negev airlift. A strip of farmland fifteen hundred feet long was pancaked down by whatever equipment could be mustered. On this strip DC-3 planes piloted by South Africans landed after dark to evacuate the wounded. Every attempt at landing was not successful because of Egyptian crossfire. The field was six miles from the hospital (over impassable roads by American standards), and this trip the wounded men made on the floor of trucks. Frequently this shuttle had to be made several painful trips before the plane was able to land. The forbearance and deep suffering of the patients is a story that left a deep and lasting imprint on me. During all these trying days most of us had lost an average of forty pounds in weight. When the Givati Army from the Jerusalem sector came down to help us the Palmach was flown back to Tel Aviv for a well-earned rest. In the final phase of the Negev battle in October the Egyptian Army and air force were completely destroyed, the Negev was a secured part of Israel, and military hospital number one ceased to exist in reality and ascended into the limbo of memory.

Trouble was brewing in Galilee. To apply the lessons learned by bitter experience I was asked to prepare the surgical service in Haifa. The transition from the Negev to the Galilee was a seventy-two hour respite in Tel Aviv spent in the dorsal decubitus position as I relinquished myself to the anonymity and oblivion of sleep. The bitterness that the British Colonial office had engendered in me by a third of a century of duplicity, tyranny and murder-for-the-sake-of-British-imperialism (Crum: Behind the Silken Curtain and Granados. The Birth of Israel, are must readings) mounted to a new high when my eyes beheld the handiwork of English vindictive minds in Haifa. They abandoned the Italian hospital in Haifa early in May (their 42nd general hospital during World War II)—abandoned it to the Arabs, that is, who under English direction, demolished the operating suite, tore out all plumbing and electric fixtures, cut cables of the elevators—in general, created a shambles. By the time we were scheduling several cases each morning the general military situation (Israel chased the Northern Arab army including Lebanon out of the land in 72 hours) another move was necessary. This move was dictated by the fact that not only the roads of the country were in Israeli hands but the Israel air force now ruled the skies from Cairo to Lebanon. The Jerusalem sector had been brought under control largely by virtue of the Burma road, a stretch of road twelve miles long built around the infamous Latrun pumping station. This station which supplied water to Jerusalem was bombed by the Arab legion, and was never replaced due to half-hearted orders of the United Nations that no one seemed enpowered to enforce. The incomparable heroism of those who built the road and laid down a ten inch water line as they proceeded, under constant fire and daily casualties, is not easily for-

gotten. They saved the people of Jerusalem from capitulation to the Arab legion, a fate worse than starvation—as proved by the Arab legion more than once—at Kfar Etzion, Midya, etc.—where my eyes bore witness that our prisoners were decapitated after capture.

Six miles east from Tel Aviv, just off the main road now lives a vibrant, growing giant that means much in the life of Israel. Tel Litwinsky hospital consists of sixty-five white one story buildings and is sprawled over the gentle rolling plains that lie between the seashore to the West and the mountains to the East. It gives one the impression of a large American army general hospital—because that is exactly what it was in 1943. The English, who used it from 1945, gave it the same treatment they extended to the Haifa Hospital early in May, 1948, before their withdrawal. Now the time was ripe for Tel Litwinsky to become the central hospital for definitive surgical care. Surgical personnel was regrouped bringing the chiefs of service together at this center—Dr. Spira in orthopedic surgery (trained in Prague), Dr. Pauzner in Thoracic Surgery (trained in Israel and Boston), and myself in abdominal surgery. With all hands and stations working at an inhumanly feverish tempo, increasingly extensive service was rendered to the battle casualties—and the hospital grew by leaps and bounds. A necessary and concomitant portion of this lightning rapid growth was the great wealth of surgical equipment from the United States and Canada. During the latter stages of the war Tel Litwinsky hospital cared for seventy-five per cent of all seriously wounded throughout the extent of the Republic. In no case did more than eight hours elapse from the time of wounding until the patient arrived in the operating theater of this hospital.

Medicine After the War

Tel Litwinsky has grown according to expectation. It includes today the finest chest surgery center in the entire middle east. In addition to all the thoracic and thoraco-abdominal injuries of wartime, it has become the center for surgery of tuberculosis, pneumonectomy, lobectomy, segmental resections are daily to be found on the operative schedule. The central service for all paraplegics in the land has also been set up at this institution. The unprecedented rate of immigration to Israel has added a new but not unexpected strain and responsibility to the physical plant and personnel respectively of this growing medical giant. The necessity for expansion with all of its attendant demands mounts daily, the completion of the rehabilitation center for amputees and numerous other categories of casualties become daily more urgent. The new chest surgery service is hard pressed to care for the all-too-many who must have immediate care amongst the recent arrivals from Europe. There are still one thousand known cases of tuberculosis in Europe yet to be received. With all of this there is a shortage of trained nurses, the only possible solution to which is more nurses' training schools.

To the perseverance, genius, self-denial and farsightedness of Dr. Harry Heller more so than to any other single factor, medicine in Israel will be on a par with the finest standards in the world. It is he who built the department of medicine of the Kupat Cholim, he guided the destinies of Tel Litwinsky hospital (those of us who were with him from the start fondly call it Heller's Hospital), he introduced the technic of sending capable young men to the United States for advanced training, and his philosophy of medical education has become the standard of the land. The new medical school at the University of Jerusalem, Hadassah sponsored, is in the process of building a faculty whose nucleus will come from the United States and England. It will not be easy to match the excellence of the staff at Tel Litwinsky where Dr. Heller is now Chief of Medicine. The name of Tel Litwinsky hospital may soon be changed to Rambam hospital in honor of Maimonides, the great Jewish physician (1135-1204). Clearly this modern medical miracle need not and will not supplant or replace existing medical installations. It is complementary to all existing systems of medicine; it is operated by the government of Israel. The high esteem in which this budding medical colossus is held is attested to by the fact that Kupat Cholim and Hadassah have recent-

ly both made overtures to the government to acquire it.

The Tel Litwinsky hospital has secured for itself a place of distinction in the annals of Israel's birth and in its life in the future. Her portals will always be open to the veterans of their country's war for independence, and her arms shall always welcome and care for the medically needy who have returned to seek refuge in the land of their fathers. The institution was built for and exists for them; the process of building was and is a labor of love. The people who succeeded in erecting this medical monument were moved by a moral strength, clarity of purpose and directness of approach that IS the Israeli spirit. I shall be forever grateful for the enriching experience that has come to me with the historic opportunity and privilege to give of myself to them and to receive the exhilaration of that spirit in return.

MILKSICKNESS — AN ADVENTURE IN DIAGNOSIS

HUGO R. RONY, M.D.*

I first saw the patient 2 years ago in my office. He was 43 years old, a farmer, married for 20 years; they have 3 children. He had been ill the past 2 months. The main complaints were loss of appetite with loss of weight and weakness. Some days he would eat quite normally but most of the time he not only lacked appetite, but had an aversion to food: smelling food would make him nauseated and even caused vomiting. He lost 15 pounds during these 2 months. There was a feeling of fullness in the upper abdomen much of the time but no pain in the abdomen or elsewhere. The bowels were regular with apparently normal stools. His muscular weakness became progressively worse and at times—especially when he tried to do some work out on the field under the sun—it was profound: "I just stand there, trembling," he said. There were no other complaints. He had no fever, he slept well, didn't feel nervous or anxious, there was no dizziness or feeling of fainting. He is not a drinking man, never was. He used to be a moderate smoker—gave it up about 1 month before his visit. He had never been sick in bed as far back as he could remember. The family history was not remarkable. His family physician examined him several times, X-rayed his stomach and gall bladder and announced that he did not know what was wrong with him. He then went to a prominent diagnostic institution and was told that he had a "nervous stomach."

The patient was a well developed, ruddy faced man with the calmness and earthy intelligence of a "typical" midwestern farmer. His weight was 161 lbs. which was quite normal for his height. Careful physical examination in the office, including rectal examination, fluoroscopy of the chest and retinoscopy, yielded normal findings throughout. The blood pressure was 110/80, the pulse was regular, the pulse rate 90. Dynamometer tests of his muscle power showed that his grip was not too weak, although probably 20 to 25 per cent weaker than one would expect of a man his build and occupation. The erythrocyte count was 4.5 million, hemoglobin 90%, white blood cells 7000. The sedimentation rate was normal. The urine contained no albumen or sugar and the sediment contained no pathological elements.

The general impression I had in looking and talking to this man did not support the idea that he suffered from a psychosomatic disturbance; in fact, he impressed me as the very antithesis of the neurotic-appearing personality. Nevertheless, I entered into a thorough discussion with him about his past and present emotional life; in this I obtained his calm and intelligent co-operation. No particular worries, anxieties, frustra-

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tions, insecurity or other potentially disturbing factors seemed to be present; he was well off financially, his marital and family life was reasonably happy. (Later I talked to his wife and brother and they corroborated these statements.)

Could there be some kind of toxicosis such as lead, arsenic, DDT, carbon monoxide, carbon tetrachloride? The rest of the family were in good health, he hasn't been handling such materials and the symptoms did not seem to be typical of these or other poisons that I could think of. Could food allergy produce such a clinical picture? He was eating the same varied, natural, wholesome diet he always ate, no new foods have been added, he never had any allergic manifestations, neither had anyone in his family.

There was, of course, the possibility of some serious organic disease such as Hodgkin's, aleukemic leukemia, retroperitoneal malignancy, pituitary or adrenal atrophy or chronic infections such as brucellosis, etc. I urged him to enter the hospital for a complete study, and he did 2 weeks later. During 3 weeks in the hospital his temperature, pulse and respiration were normal. Tests included careful blood cytology, blood Kahn, gastric content analysis, complete G.I. X-ray, intravenous pyelography, chest films; sedimentation rates, metabolism tests, EKG; blood NPN, urea, chloride, calcium, phosphorus, glucose, cholesterol, albumin and globulin, alkaline phosphatase, cephalin flocculation; stool examinations for occult blood, ameba and ova; agglutination tests for salmonellae and brucella, and skin tests with brucellergen. No pathological alterations were found in any of these tests except in the EKG which was interpreted as "probably abnormal graph suggesting right ventricular strain." Sternal puncture was refused by the patient who began to feel better soon after he entered the hospital; his appetite and strength improved, he had none of the peculiar "weak spells," and gained 3 lbs. He left the hospital without a definite diagnosis. Maybe it was a gastric neurosis after all, I thought, improving as a result of "removal from his environment." I asked him to return to the office in a couple weeks.

When I saw him next, 4 weeks later, he looked sick and discouraged. All symptoms returned soon after he left the hospital, he now felt weaker than ever, lost 5 lbs. A painstaking physical examination again failed to reveal any abnormality. I was about to tell him that he must go back to the hospital for a sternal puncture and, possibly, an exploratory laparatomy, when he said, quietly: "Doctor, I know you are looking for some kind of a clue, and I reckon patients are telling you all kinds of silly things, but maybe this will help you. About a year ago, not far from where I live, a farmer got sick, couldn't eat, was awfully weak and shaky-like—just as myself—and died. The doctors couldn't find out what was the matter with him, but I heard later that one doctor said that he must have died from milk sickness. I told this to the doctors when I was up there in that Clinic, but they laughed it off. What do you think?"

Milk Sickness! I had a vague recollection of a rare disease—I must have read about it some place years ago—that one can get from the milk of cows that were eating some poisonous plant. I pulled off the shelf Osler's Principles and Practice of Medicine. There it was: Milk Sickness. I read the chapter, asked the patient a few questions, examined his urine for acetone—it showed 1+ reaction, gave him some advice—especially to stop drinking milk and eating butter and cheese, and told him to come in again after a few days. In the meantime, I would look into this milk sickness in more detail.

* * *

Early in the 19th century, an insidious disease struck at settlers and their cattle in some parts of Ohio, Illinois, Indiana and Kentucky, forcing many pioneers to abandon settlements and leave behind them deserted cabins and fresh-turned graves. Hardy frontiersmen knew what it meant when their cows trembled and died, and when weakness, trembling, loss of appetite and vomiting fell upon their families. They recognized early that the disease was endemic in certain areas, but did not occur in others, that

it originated in the cattle and was transferred to people through the milk they drank. They called it the "trembles," "sick stomach," the "slows," but mostly they called it "milksickness." There were many other theories concerning the cause of this disease, such as poisonous minerals in the soil or in the drinking water, but by the middle of the 19th century it was generally believed that humans became milksick only after drinking milk from cows which had been poisoned as the result of eating some unknown plant. There was no agreement, however, among settlers and doctors as to which plant was the active agent, although as early as 1838 a farmer in a published article announced that it is the "white snakeroot." But, it was no before 1906 that it was demonstrated in the laboratory that white snakeroot, *Eupatorium ageratoides,* when fed to animals, resulted in the "trembles." Finally, in 1917, J. F. Couch, a pathologist of the Bureau of Animal Industry, extracted an active poison from the leaves of the white snakeroot, named it "tremetol" and identified it as an aromatic alcohol, $C_{16}H_{22}O_4$. It was also demonstrated that the Rayless goldenrod, a weed of Western Texas, New Mexico and Arizona where milk sickness also occurs, contains tremetol. These weeds — and milksickness — are unknown outside the U.S.A.

The white snakeroot thrives best in dry years in thickly wooded ridges near small streams where cattle may move for protection from heat and flies. The animals eat the leaves containing tremetol and may develop the trembles. Milch cows tolerate considerable amounts of the poison without becoming sick because they can excrete it in their milk; but their calves become sick and may die or persons consuming the milk, butter or cheese made from the milk, may contract the disease. Pasteurization does not destroy the poison. However, there is little or no danger from the use of dairy products produced by mixing the milk of many farms, as the poison which may get into the milk from one source is in this way so much diluted that it is rendered harmless; for this reason the disease is practically nonexistent in city population.

Milksickness that has wiped out whole communities in this country in pioneer days is rare now, although 21 cases had been reported in Illinois as late as 1937-1938. Most cases occur in late summer and early fall but some had been observed at any season of the year, even winter. Mortality is high—about 20% in those sick enough to call a doctor. Especialy dangerous is the **acute form** which frequently kills in 2 to 9 days. The symptoms are: total lack of appetite, nausea, continuous vomiting, prostration, intestinal stasis, subnormal temperature, irregular pulse, extremely low blood pressure, fetid breath, acetonuria. Autopsy findings show marked injection of the blood vessels in the mucous membranes of the stomach and intestines, and fatty degeneration of the liver. In the **subacute and chronic forms** the symptoms are similar but differ in degree. It is said to be characteristic for these forms that the patient may feel quite well for some days only to relapse with an attack of weakness, trembling, nausea and vomiting after muscular strain or exposure to heat. **Diagnosis** must be made from the history the general clinical picture and the lack of other demonstrable cause. There are no specific physical or laboratory findings except, possibly, acetonuria (especially in the more acute forms) and hypercalcemia that has been recently reported in some cases. There is no specific **therapy** except to omit dairy products in the diet in any form. The patient must be kept at rest, and the acidosis and dehydration treated with high carbohydate diet, intravenous glucose, etc., as in other forms of acidosis. Recovery may be slow and relapses may occur many months later.

* * *

I concluded that the patient was suffering from a chronic form of milksickness in view of the following features of the case: 1) All symptoms, especially the trembling and the deleterious effect of exercise and exposure to heat were consistent with this diagnosis. 2) Careful examinations and extensive laboratory tests failed to disclose other possible etiology. 3) Patient had acetonuria on the one occasion we looked for it. 4)

He immediately began to improve when he stopped drinking his cow's milk, which probably was also the reason of his temporary improvement during his stay in the hospital. Gradually, he completely recovered but had a few "weak spells" even the following summer when working under the sun. Grundy County, where the patient lives, is one of the few counties in Middle and Northern Illinois where milksickness used to be endemic and from where sporadic cases of the disease have been reported up to the present time. 6) He told me, on questioning, that he was regularly drinking the milk of one of his cows, and of that cow's only, while the other members of his family never drank that milk. The cow seemed to be in good health, but one of his animals recently died after a brief illness that was not diagnosed at the time and which, looking back at it, might well have been milksickness. 7) As I read to him a chapter on milksickness, and showed him pictures of the white snakeroot, he told me that his cow-pasture ended in a wooded ridge, that on several occasions he saw his cattle grazing on that ridge, and that he saw weeds there that looked like those shown in the pictures. Later, on my request, he brought in a couple of these plants. They showed all the botanical characteristics of white snakeroot. I took them to the Department of Botany, Univ. of Illinois, where they were definitely identified as *Eupatorium ageratoides.*

Remember the advice the great Osler used to give to his students and associates? *"Listen* to the patient—he will frequently give you the diagnosis if only you listen to him." It was never more true than in this case; in fact, this patient unwittingly, gave away the diagnosis twice. First, when he said: ". . . and there I was *trembling."* It failed to register with me. Later, he suggested the diagnosis in so many words. That time, fortunately for all concerned, I listened.

REFERENCES: E. L. Moseley, Milk Sickness Caused by White Snakeroot. Published by Ohio Academy of Science and the Author, Bowling Green, Ohio. (1941)

CLINICAL-PATHOLOGIC CONFERENCE *

H. Faigen, Interne:

HISTORY:

A 70 year old white female was first admitted to Mount Sinai Hospital on April 24, 1943, with a history of progressive dyspnea on exertion for the past three or four years; headaches, two years duration; and dizziness, two years.

PHYSICAL EXAMINATION revealed a slightly cyanotic, dyspneic, elderly woman with emphysematous chest, rales in both bases, enlarged heart, blood pressure 180/110 and a precordial systolic murmur most marked at the aortic area. The liver edge was palpable and there was moderate pedal edema associated with varicosities. The patient was discharged five days after admission with the diagnoses: hypertensive cardiovascular disease with left ventricular hypertrophy; coronary sclerosis with myocardial degeneration, and early congestive failure.

SECOND ADMISSION. The patient was readmitted to this hospital on June 3, 1944, with complaints of coughing and pain in the chest for the past three weeks. History at that time elicited a chronic non-productive cough of many years duration and diabetes for three years preceding admission.

PHYSICAL EXAMINATION at that time revealed a cyanotic woman with emphysematous chest, enlarged heart, no cardiac murmurs, considerable purulent expectoration and many crackling rales in the bases posteriorly. There were also crackling rales in the left upper lobe. Temperature at that admission was 101.4 but returned to normal twenty-four hours after admission. The temperature remained so until patient was discharged eleven days later with the diagnosis of chronic bronchitis, pulmonary emphysema and cor pulmonale. While in the hospital, the patient received aminophyl-

* From the current files of Mount Sinai Hospital, Chicago, Illinois.

lin and digitalis. Laboratory findings were normal.

The patient was admitted to another hospital on September 25, 1948, with chief complaints of inability to eat, vague pains, loss of strength, and marked loss of weight in two weeks. X-ray revealed a Colles' fracture of the right wrist. She was discharged improved on October 9, 1948, with a diagnosis of malnutrition and senility.

THIRD ADMISSION. Patient's final admission here on November 4, 1948. The chief complaints on this admission were rapid weight loss, weakness, alternating periods of diarrhea and constipation, abdominal cramps, marked pain in the back and not being able to stand or walk for fear of falling. Prior to this admission, the patient had been running a fever of 102 to 104 daily and complained of "hot and cold sweats," marked thirst and frequent coughing spells which were productive of a thin watery mucus. The patient also complained of severe headaches, pain in the left ear and marked skin sensitivity. There was a history of tarry stools on at least one occasion. There was no history of vomiting or hematemesis. The history was obtained from the daughter and a practical nurse. The temperature on admission was 103.4, pulse 136 with occasional extrasystoles, respiratory rate 48, blood pressure 122/58.

PHYSICAL EXAMINATION revealed a thin, dehydrated, elderly female. The skin was hot and dry. Turgor was poor; complexion dark with pigmented areas of previous psorasis. The patient had marked cutaneous hyperesthesia over all bony structures. The pupils were small, round and equal and did not react to light. There were some small shotty posterior cervical glands. The tongue

Laboratory Findings

Blood Counts	RBC	WBC	Hb.	Color Index	Stabs	Segs	Eos	Lymph	Mono	Meta	Myelo
4-26-43	5,250,000	3,900	87%	.9		53		37	10		
6-5-44	4,490,000	9,100	84%	.94	2	62	1	30	5		
11-4-48	4,020,000	14,700	69%	.86	18	22		44	12	3	1
11-8-48	4,300,000	10,700	72%	.84	8	70		8	11	3	

Blood Chemistry:	Sugar	UreaN	NPN	Creatinine	T.P.	Alb.	Glob.	A/G Ratio
4-26-43	115	14		5.0				
6-5-44	120	12						
9-27-48	166	40						
11-5-48	222	18			7.6	4.8	2.8	1.7/1
11-8-48	380	42	64	2.95				

Urinalysis:	React.	Sp. Gr.	WBC	RBC	Casts
4-28-43	acid	1.008			
4-26-43	acid	1.010			0
6-5-44	alk.	1.020			0
6-6-44	acid	1.012			
6-13-44	alk.	Q.N.S.			
11-5-48	acid	1.020	0-1	0	0
11-6-48	acid	1.021	3-5	0	finely & coarsely granular.

4-26-43 Serologic test for syphilis: Negative
6-5-44 Serologic test for syphilis: Negative
11-5-48 Serologic test for syphilis: Negative
6-5-44 Examination of sputum for tubercle bacilli: None seen.
11-6-48 Hematocrit: 44
11-6-48 Smear from mouth for blood: Gross: negative
Benzidine: faint trace.

was smooth and red. There were numerous crepitant rales in the right base and in the right axillary region. The patient was placed on crysticillin, 300,000 units twice daily. On the second hospital day, she complained of sudden severe pain in the back. Examination detected bronchial breathing in the right lower lobe with a pleural friction rub in the right infra-axillary region. The temperature dropped on the 4th hospital day and was normal. However, the patient was still incoherent and still showed signs of consolidation of right lung. On the 5th hospital day, respirations became more labored, pulse was 160 and bronchial breathing appeared on the left side. The patient was placed on streptomycin, fluids and nasal oxygen. However, she continued a down hill course. The temperature rose to 105.2 and the respiratory rate to 60. The patient appeared ashen blue, non-responsive and expired at 11:45 A.M. on November 9, 1948.

Dr. M. Kirschen, Attending Physician:

I saw this patient for the first time in consultation at her home. The attending physician was not present at the time of the examination and I had no history whatsoever. I was told that the patient had returned home a few days ago from another hospital where she had been for two weeks. She felt weak for months, was running a temperature, and had a constant diarrhea with occasional tarry stools. The course in the hospital was rapidly downhill and the patient expired after five days. She was incoherent, semi-conscious and because of the gravity of her condition we had neither time nor opportunity to study her extensively. On the basis of her history, appearance and clinical findings we were thinking mainly of two things: a blood dyscrasia, or a gastro-intestinal malignancy with metastases. The diagnosis of carcinoma of the right colon was enticing, especially since a similar case presented here at one of the last conferences proved to be a carcinoma of the cecum at post mortem examination.

Dr. J. Arendt, Radiologist:

A thorough roentgentologic examination would have been indicated in this case; I assume that films have been taken either on the outside or in another hospital. We here saw the patient only once in a terminal stage. We had here a typical "oxygen tent film," with dense infiltration of pneumonic-atelectatic character and large hilar vessels and probably large hilar glands. A marked aortic sclerosis is compatible with the age of the patient. Further analysis of the multiple lung infiltrations as to malignancy was not possible at this stage.

Dr. I. Davidsohn, Pathologist:

The body was in a poor state of nutrition. The main lesion was in the abdomen. Large masses of lymph nodes were found near the bifurcation of the aorta (Fig. 1) and in other parts of the abdomen. The aorta showed advanced atherosclerosis. The enlarged lymph nodes were matted together, soft, with a smooth glistening section surface. The gross appearance was that of a lymphosarcoma or lymphocytic leukemia, or, though less likely, Hodgkin's lymphogranuloma. In addition to the periaortic lymph nodes those similarly and strikingly enlarged were the perigastric and peripancreatic. The superficial lymph nodes were not palpably enlarged except for a few axillary lymph nodes measuring up to 5 mm.

Microscopic findings: In some lymph nodes the general architecture was fairly well preserved but in several places atypical large giant cells were seen with dense hyperchromatic nuclei. The reticulum was also increased. In other lymph nodes much more advanced changes were found. The normal architecture with the normal distribution of reticulum and lymphocytes was completely replaced by infiltrating large atypical cells showing considerable variation in size and shape. The reticulum was greatly increased (Figs. 2, 3). The findings were interpreted as a reticulum cell lymphosarcoma. In some sections there was invasion of blood vessels by tumor cells. Many atypical mitoses were present.

This type of a lymphatic neoplasm is being diagnosed by some as Hodgkin's sarcoma. Personally I favor the diagnosis of reticulum cell sarcoma. There are

PLATE I

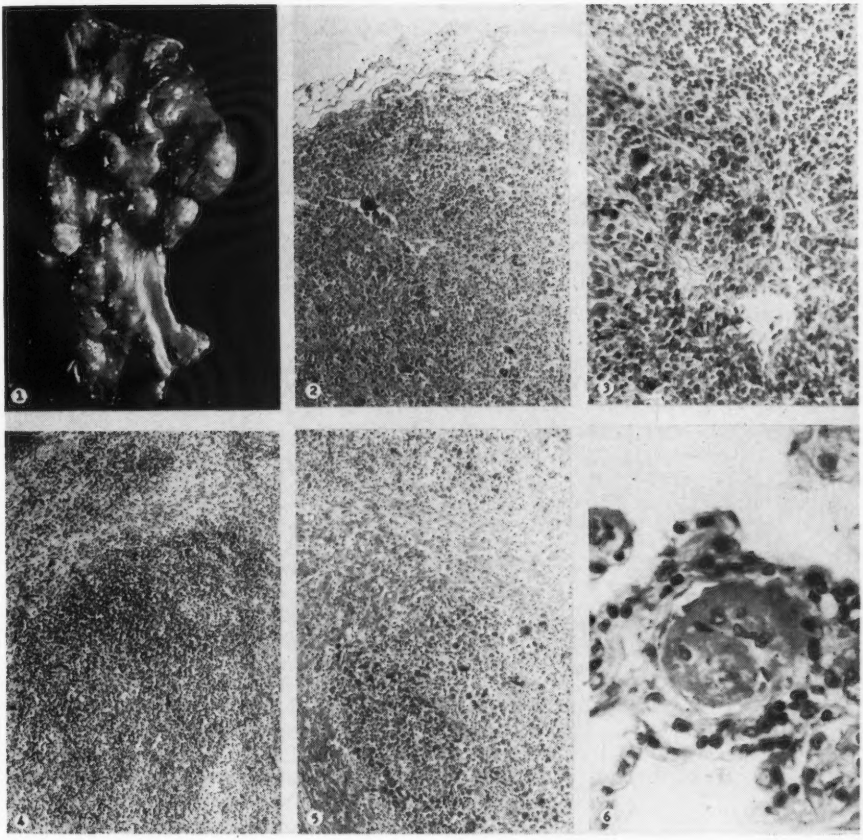

Fig. 1. Large masses of enlarged lymph nodes surrounding the aorta and accompanying the common iliac arteries.

Fig. 2. Lymph node. Neoplastic tissue completely replaces the normal architecture. Note the numerous giant cells. Photomicrograph. X 100

Fig. 3. Same. Higher magnification. Note bizarre shape of giant cells and increase of reticular fibers. Photomicrograph. X 250

Fig. 4. Mediastinal lymph node. In contrast to Fig. 2 and 3, part of the normal lymphoid structure is preserved. Note beginning infiltration by reticulum cell sarcoma. Photomicrograph. X 100

Fig. 5. Liver. A rather sharply demarcated metastatic lesion. The morphology resembles closely that of the primary tumor in the lymph nodes. Photomicrogaph. X 100.

Fig. 6. Lung. Thrombus occluding a small blood vessel. Such findings frequently are the result of the trapping of embolized cells (e.g., tumor cells) in the pulmonary circulation. Photomicrograph. X 600

those who fail to see any essential difference in these two terms.

The liver was the site of many metastases in the form of small circumscribed nodules on the outer and on the cut surfaces. Microscopic sections showed replacement of liver parenchyma by a typical anaplastic tumor cells similar to those seen in the lymph nodes (Fig. 4).

The spleen was enlarged, weighing 350 Gm., and showed roughly similar changes as the liver but less pronounced. Microscopic sections showed circumscribed areas of metastases surrounded by more or less normal splenic tissue.

Metastatic nodules were present also in the vertebrae, sternum, and in other bones.

The marrow in between the metastases was remarkably well preserved.

It is quite possible that a sternal puncture could have helped to establish the correct diagnosis. Sternal marrow smears prepared at the autopsy showed the typical lesion.

The neoplastic process was most active in the abdomen and bones. In the mediastinum only small anthracotic lymph nodes were found with indistinct yellowish white areas, grossly suggesting metastatic involvement, which was confirmed by microscopic examination (Fig. 5), but even here the process was less advanced than below the diaphragm.

In the left main bronchus just below the bifurcation there was a narrow fistulous tract perforating the wall of the bronchus and leading into an old broken down tuberculous lymph node which was attached to the outer circumference at the site of the perforation.

Lung: Some of the small blood vessels were occluded by thrombi in various stages of organization (Fig. 6). It is very possible that these thrombi represent reactive changes to tumor emboli, in this case, lymphosarcoma cells. It is well known that tumor emboli may be responsible for such changes in the small blood vessels and capillaries of the lungs which have a tendency to intercept abnormal cells from the circulation. For example, megakaryocytes which have left the bone marrow may be caught in the capillaries of the lung. I am, of course, aware of the fact that according to some authors megakaryocytes are normally present in the lungs and that blood platelets are produced in this organ in addition to, or even to the exclusion of, the bone marrow.

I want to discuss briefly the terminology of neoplasms of lymphatic tissue. There has been a deplorable confusion in the terminology of these lesions. Table I lists only some of the terms that have been found in the literature. Not all have been included. For example, at least three or four other terms are being used for giant follicular lymphoblastoma.

There is little doubt that some of the confusion is due to the fact that authors have attempted to classify, possibly too sharply, conditions which are not classifiable because they are different stages in the development of a single lesion. These stages of development manifest themselves by various degrees of differentiation. Another source of confusion is the application of imperfect knowledge to classification. For example, some authors consider Hodgkin's lymphogranuloma an inflammatory process, others claim that it is a neoplasm, to begin with, and others that it becomes a neoplasm in the terminal phase of the disease. Application of this imperfect knowledge to classification is an obvious further source of confusion.

I think it will help to understand neoplastic lesions of lymph nodes if we re-

Table 1

TERMINOLOGY OF LYMPHOBLASTOMAS

Lymphoma	Lymphoid leukosis	Leukosarcoma
Lymphocytoma	Leukemic and aleukemic lymphadenosis	Pseudoleukemia
Lymphosarcoma	Hodgkin's disease	Endothelioma
Lymphoblastoma	Hodgkin's sarcoma	Reticulosarcoma
Follicular lymphadenopathy	Lymphadenoma	Reticulosis
Giant follicular lymphoblastoma	Lymphagranuloma	Reticulo-endotheliosis
Lymphatic leukemia		Mycosis fungoides

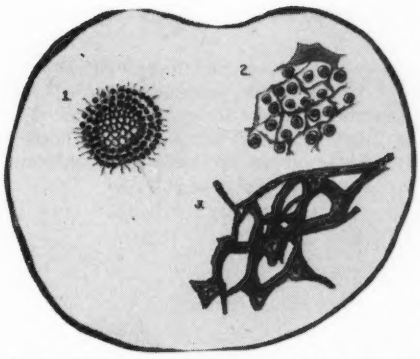

Fig. 7. Schematic presentation of the components of lymphatic tissue. 1—lymph follicle, 2—reticulum, 3—endothelial cells lining blood vessels or lymphatics.

view briefly the general structure of lymphoid tissue (Fig. 7). There are only four main components from which neoplasms can originate; 1. lymphocytes, and their precursors lymphoblasts; 2. reticulum; 3. endothelial cells; and 4. fibroblasts or fibrocytes. The first two are most important. Lesions originating from endothelial cells are rare and still less frequent are lesions originating from fibroblasts.

The lymphoid tissue is basically a network of reticulum which holds in its meshes mature lymphocytes and in some places young precursors of lymphocytes, lymphoblasts. The accumulations of lymphoblasts in the form of nodules are the so-called germinal centers.

The reticulum is actually a syncytium without sharp lines of demarcation of the individual cells with nuclei irregularly distributed in the syncytial mass. The reticulum is the matrix or stem tissue from which the normal elements and all neoplasms of the lymphoid and reticuloendothelial tissues develop.

The most frequent neoplasms of lymphoid tissue can be divided into two groups: one, which originates from lymphocytes: lymphocytic lymphosarcoma, or if its cells are less differentiated, lymphoblastic lymphosarcoma. The second group originates from the reticulum: reticulum cell lymphosarcoma which again can be subdivided according to degree of differentiation. If the structure is that of a syncytium then it can be called a syncytial type of reticulum cell lymphosarcoma, and so on.

The differentiation into these two main groups has considerable practical value, first with regard to prognosis in general, and especially with regard to response to radiation. As a rule, reticulum cell lymphosarcomas are more frequently generalized at an earlier stage than the lymphocytic type of lymphosarcoma. The latter as a rule is more frequently localized and remains so for a longer period of time. The response to radiation is probably somewhat more satisfactory and more prompt in the lymphocytic type.

ANATOMIC DIAGNOSIS: PARAAORTIC LYMPH NODES: Lymphosarcoma, reticulum cell type, primary; ILIAC, PERIPANCREATIC, PERIGASTRIC AND PERIPORTAL LYMPH NODES: Lymphosarcoma, reticulum cell type; MEDIASTINAL LYMPH NODES, SPLEEN, LIVER, STERNUM, VERTEBRAE: Lymphosarcoma, reticulum cell type, metastatic; HEART: Brown atrophy; calcification of mitral ring; coronary sclerosis, slight; fibrosis of myocardium, slight; AORTA: Atherosclerosis; LUNGS: Emphysema; suppurative bronchitis; focal atelectasis; multiple vascular thromboses; KIDNEYS: Parenchymatous degeneration; BRAIN: Senile atrophy; UTERUS: Senile atrophy; OVARIES: Fibrosis; serous cysts. CACHEXIA.

Dr. M. Kirschen: Was there any involvement of the intestines to explain the bleeding?

Dr. I. Davidsohn: No, there was no involvement of the intestines at all. The only organs involved were those mentioned. I have the impression that the tumor originated in the abdomen and in the retroperitoneal lymph nodes and that from there it metastasized to the spleen, liver, bones and mediastinal lymph nodes.

Dr. Kirschen: What is the explanation of the bleeding?

Dr. Davidsohn: There was a fistulous tract resulting from a perforation of the wall of the left bronchus into an adherent old tuberculous lymph node. That could have been the source of some bleeding.

CURRENT COMMENT

ANTI-HISTAMINIC DRUGS

The presence of hypersensitiveness in man has been recognized since before the time of Christ. Galen described allergy to goat's milk and the Babilonian Talmud gives detailed directions on the treatment of egg allergy by giving appropriate doses of egg albumen. The scientific phase of our knowledge on allergy started with the work of Richet, who introduced the word "anaphylaxis," meaning "the removal of protection," and of V. Pirquet who coined the word "allergy" or "altered capacity to react."

In 1910 Barger and Dale isolated histamine from ergot, and Dale observed that the effects of this drug in animals closely resembled anaphylactic shock. Later Dale propounded the theory that histamine is liberated from the tissue of animals during the shock and is responsible for the symptoms of anaphylaxis. According to this theory the exposure of a patient to the allergen produces the formation of antibodies called "reagins." The latter react with the antigen and, as a consequence of this reaction, the patient's cells are injured and histamine is liberated. This results in capillary dilatation, spasm of the smooth muscle, and cutaneous, respiratory, gastro-intestinal and other symptoms, depending upon the main site of histamine liberation.[1, 2]

The therapy of allergy is based on this theory and follows two main rationales. The first type of therapy consists in desensitization of the patient to the allergen. According to most authors, desensitization consists in the artificial production of blocking antibodies which prevent the antigen-antibody reaction and, therefore, the liberation of histamine. The second type of therapy consists in neutralizing the effects of histamine once the latter is liberated by the tissues.

Neutralization of the histamine effects can be accomplished in two ways. The first one is the use of drugs which have opposite pharmacologic effects. For instance, the use of sympathomimetic drugs to offset histamine vasodilation and to dilate the bronchi constricted by histamine (epinephrine, ephedrine, theophilline). This type of therapy is similar in principle to the use of antidotes in the therapy of certain types of poisoning. More recently there have been introduced into the pharmacopea a number of drugs capable of neutralizing histamine itself by blocking it at its sites of action. Instead of counteracting its effects, these drugs would tend to prevent them.

The first "anti-histaminic" drug was discovered by the French workers Fourneau and Bovet and called 929-F. Later Bovet and Staub[3] described a similar drug, 1571-F. Both drugs were too toxic for clinical use, but were the starting point for the synthesis of a large number of other compounds which led finally to the discovery of the first effective and practical antihistaminics: antergan, described by Halpern,[4] and neoantergan, described by Bovet and collaborators.[5] Since the synthesis of these two compounds many more have been synthesized and at least 12 of them are now commonly available, giving the physician the possibility of choosing the one best suited to the individual case. This is a fortunate circumstance as one patient may respond to one drug and not to another, or one drug may give undesirable side reactions in one patient and not in another.

All antihistaminic drugs are capable of preventing the effects of histamine on the isolated intestinal loop and of preventing anaphylactic shock and bronchospasm in the guinea pig. They appear to be of definite therapeutic value in 70 to 80% of the cases of allergic rhinitis and urticaria, in 20 to 75% of the cases of allergic asthma and in a variable number of cases of other types of allergic manifestations. In 10 to 25% of the cases, one or the other of the antihistaminic drugs will give undesirable side effects, such as: drowsiness, vertigo, nausea, headache, mouth dryness, gastro-intestinal upset, palpitation, excitation and

nervousness. Usually one drug can be found which will give no side effects in the individual case.

It has been reported recently that the antihistaminic drugs are of value in the treatment of the common cold,[6] but this report has not been confirmed as yet.

As a result of the search for new antihistaminic drugs, another very interesting compound has been synthesized. This is Dramamine, a potent drug in the therapy and prevention of motion sickness. A clinical experiment on 1,376 men in an army transport revealed that Dramamine prevented motion sickness in 98% of the cases and cured completely 97% of the cases in another group.[7]

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COMPOUND E

It has been the impression of many clinicians for many years that rheumatoid arthritis improves dramatically during pregnancy and during the course of hepatitis with jaundice. This fact has been recently confirmed by Hench.[1] Although no explanation of the phenomenon is available, the observation is of great importance as it demonstrates that the disease is not necessarily progressive and irreversible and because it suggests the possibility that rheumatoid arthritis might not be of microbic but rather of biochemical origin. Many attempts have been made to reproduce the beneficial effects of pregnancy by the use of female sex hormones and those of hepatic jaundice by the use of bile salts and pigments, but all have failed. Recently, however, the hopes for an efficient therapeutic agent have been revived by the work done at the Mayo Clinic which resulted in the use of Compound E.

The history of compound E dates back to its isolation from the adrenal gland by Kendall in 1937. Shortly theeafter, Ingle showed that Compound E has a marked effect on muscular activity and other investigators found that it influences carbohydrate metabolism, increases the resistance to cold, to other stresses and to certain toxic substances. Its chemical composition was found to be 17-hydroxy-11-dehydro-corticosterone. For many years research on the physiological properties of Compound E were limited by great difficulties in preparing the substance and no work could be done except on rats. In 1948 a practical method for its preparation was finally devised as a result of the combined efforts of the Kendall group and the chemists of Merck & Co.[2] The method consists of a partial synthesis involving approximately 30 separate chemical reactions and it is said to be one of the most complicated methods of pharmaceutical chemistry. Despite these technical difficulties, however, Compound E is now available in sufficient quantities for a satisfactory clinical trial.

P. S. Hench and collaborators[3] reported recently on the first 14 cases of rheumatoid arthritis treated exclusively with Compound E. In all cases there was a prompt and marked improvement of the clinical features of the disease and of the sedimentation rate. Often within 40 hours there was a marked improvement of stiffness. Shortly thereafter the pain on motion and the tenderness disappeared, finally the swelling was reduced and, in a few weeks the sedimentation rate returned to almost normal. At the same time there was improvement of flexion deformities, euphoria, increase in appetite and weight, improvement of secondary anemia (when present), and of insomnia. In one case, a synovial biopsy showed definite progress of healing. These improvements were maintained for as long as the treatment was continued, but, unfortunately, relapse occurred within 2 to 4 days after cessation of the injections, or when a suspension of cholesterol was given instead of Com-

pound E. There was no significant acute toxicity, although in one case, after 28 weeks of continued treatment there appeared a mild hirsutism, a rounding of the face and a complete cassation of previously irregular menses. Transient edema has been observed. It appears that symptoms of adrenal cortical hyperfunction may be produced by prolonged use of Compound E and this possibility must be ruled out by further clinical investigation before Compound E can be accepted as insulin is for the treatment of diabetes.

In view of the marked beneficial effects of Compound E on skeletal muscle and fibrous tissue in rheumatoid arthritis, it was hoped that similar effects might be obtained on the cardiac muscle and fibrous tissue of cardiac valves in acute rheumatic fever. Hench and collaborators,[4] therefore, tried Compound E in 3 adolescents suffering from this disease and noticed a rapid disappearance of fever, tachycardia, polyarthritis, a return to normal sedimentation rate and electrocardiogram. Associated with this was a sense of well-being and a return of the appetite. Similar results were obtained with the adrenocorticotrophic hormone of the pituitary (ACTH).

In evaluating the future of these new therapeutic agents, one must keep in mind the danger that their prolonged use might produce symptoms of hyperfunction of the adrenal cortex and, in the case of ACTH, the danger of producing diabetes.[5]

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CANINE EPILEPSY

Canine epilepsy, often called canine hysteria or "running fits," has troubled dog owners for the past 20 years, especially if the diet of their dog consisted mainly of dog biscuits with a high carbohydrate content. Outbreaks of the disease occurred occasionally in laboratory kennels and it was one of these outbreaks that induced E. Mellanby (1) to study the problem. It was noted that the outbreak was interrupted when the source of the bread fed to the animals was changed. Mellanby discussed the problem with the miller and found that the bread presumably responsible for the disease was made of flour which had been bleached or "improved" by treatment with nitrogen trichloride, or "agene." When dogs were placed on a diet containing large quantities of bleached flour they rapidly developed symptoms of canine epilepsy and hysteria. Within a day or two the animals changed their personality and attitudes: gentle and playful dogs became vicious and aggressive, aggressive ones became meek. Soon they underwent attacks of hysteria consisting of running fits during which the animals would bark, overturn the food containers and make a shamble of their cages. This was followed by a period of ataxia and, occasionally, by a true attack of grand mal with loss of consciousness, running or paddling movements, salivation, clonic convulsions and loss of urine and feces. The attacks were followed by a period of profound dejection and in about half an hour the animals would return to normal. If the attack lasted more than 30 minutes they were usually followed by death. The work of Mellanby was confirmed by Silver and collaborators. These investigators found that if the administration of the bleached-flour diet was continued a status epilepticus could often be produced. They also noted that the electroencephalogram of the dogs before and during the attack was practically identical with that of human epileptic patients.

Moran found that agene reacts with the protein fraction of wheat flour to produce the epileptogenic factor. These results were confirmed by Newell and collaborators. The latter investigators fed agenized wheat products to human volunteers for 2 to 4 weeks, but were unable to produce any symptoms or any change in the electroencephalogram. A mixture of

pure amino acids similar in composition to the gliadin of wheat could be converted into a convulsant by treatment with agene: 5 minutes after the intravenous injection of the treated amino acids a typical grand mal seizure was produced (6). Of 13 amino acids tried only cystine and cysteine become active when treated with nitrogen trichloride (2). It appears that breathing a mixture of 20% CO_2 and 80% O_2 precipitates the seizures and accentuates existing EEG abnormalties (7).

Animals fed on a bleached flour diet are more susceptible to metrazol convulsions. The fits are controlled by phenobarbital, but not by diphenylhydantoin and trimethadion. In this canine epilepsy differs from human epilepsy, it differs also by being associated with hysteric behavior and by being unaffected by hyperventilation, alkalosis, hydration and acidosis. The two conditions are, however, very similar in their general symptomatology, in their sensitivity to barbiturates and in the associated EEG abnormalties (8).

The British and American people have been eating bleached flour products for some 20 years or more and 90% of the flour used in these products has been treated and is being treated with the agene process. No evidence is available to show that bleached flour is deleterious to man, but the possibility cannot be excluded, nor can it be categorically denied that other processed foods may contain toxic substances and that civilization may be responsible in more than one way for the increase in nervous and mental diseases.

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BOOK REVIEWS

Blakiston's New Gould Medical Dictionary. Edited by Harold Wellington Jones, M.D., Normand L. Hoerr, M.D., and Arthur Osol, Ph.D., with the assistance of an editorial board and over 100 contributors. First edition. Flexible cloth, 1294 pp., with 252 illustrations, 129 in color. Philadelphia and Toronto: The Blakiston Company, 1949.

Based upon **Gould's Medical Dictionary,** this entirely new work represents the efforts of over 100 contributors from the various medical and allied sciences—including medical physics and chemistry, dentistry, pharmacy, nursing, veterinary medicine, biology, and botany, as well as medical jurisprudence. As an innovation, the dictionary combines a system of modern phonetic respelling with syllabification, gives alternate pronunciation, and gives cross-references from definitions to illustrations. Also included are over 130 pages of special tables of arteries, veins, nerves, muscles, enzymes, etc. grouped in a special section for ready reference. Bound into the center of the book is an atlas with 252 illustrations, 129 in color. There are 3 editions, all thumb-indexed: a textbook edition for $8.50, a thin paper edition for $10.75, and a deluxe edition for $13.50. The print is large and clear, and the boldface type makes easy reading. The book is highly recommended for all medical students and physicians.

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Shearer's Manual of Human Dissection. Edited by Charles E. Tobin, Ph.D. Cloth, 286 pp., with 79 illustrations. Philadelphia: The Blakiston Company, 1949. $4.50.

The purpose of this dissecting guide is "to facilitate and enhance instruction in gross anatomic laboratories." It gives a well-organized dissection procedure for the entire body while keeping the dissected parts in as near their normal relationships as possible, so that relationships as well as individual parts can be studied. While apparently designed to be an autonomous unit, this manual should be used by the first-year medical and dental student in conjunction with any of the standard classical texts or atlases of the human anatomy, as the 79 illustrations are not sufficiently large or adequately detailed to offer the novitiate a clear understanding of the relationships involved. The type, printing and paper are excellent, and the manual is very highly recommended to those students engaged in the practical study of human anatomy.

* * *

Clinical Auscultation of the Heart. By Samuel A. Levine, M.D., and W. Proctor Harvey, M.D. Cloth, 327 pp., with 286 illustrations. Philadelphia and London: W. B. Saunders Company, 1949. $6.50.

This important and long-awaited book concerns itself with the exposition and clinical interpretation of the various heart sounds that are heard on auscultation, and for the first time, these apparently simple sounds—heard at the bedside—are discussed in detail. The clinical significance of each finding is illustrated in every case by actual sound tracings obtained from patients. Simultaneous electrocardiograms and phonocardiograms are included to illustrate what has been heard and to help visualize the points taken up in the discussion. In addition to the ausculatory findings there are many comments on related clinical conditions and the therapeutic implications involved. The book is very well written and has an excellent index. While probably too detailed for the average medical student, this book is a "must" for all internes, practitioners, internists, and cardiologists.

* * *

Handbook of Orthopaedic Surgery. By Alfred Rives Shands, Jr., B.A., M.D. Cloth, 574 pp., with 159 drawings. St. Louis: The C. V. Mosby Company, 1948. This new edition by Dr. Shands includes the latest developments in orthopedic surgery which have arisen from knowledge gained during the late war. The book is primarily designed for the use of the medical student and general

practitioner, and presents the fundamental facts and principles of orthopedic surgery as briefly and concisely as possible though with sufficient detail to convey a well-rounded knowledge of the subject.

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The Clinical Management of Varicose Veins. By David Woolfolk Barrow, M.D. Cloth, 155 pp., with 58 drawings and illustrations. New York: Paul B. Hoeber, Incorporated, 1948.

This monograph, dealing with one of the most common afflictions of our population, is devoted almost entirely to the practical side of various situations as seen by practitioners. Dr. Barrow reminds the reader that his text is based on observations made on approximately 2500 patients with varicose veins, or their records—and not upon statements found in the literature. He further states that all the material in the monograph is a result of personal observation. As further assistance to the reader in making clear the problem of management of varicose veins, the physiological mechanisms involved are—with the aid of 58 drawings and illustrations — clearly explained, while controversial points are minimized. The large print and heavy gloss paper make for easy reading. The book is recommended for all practicing physicians and surgeons.

* * *

Bensley's Practical Anatomy of the Rabbit. Revised and edited by E. Horne Craigie, Ph.D. Cloth, 391 pp., with 124 illustrations, including 8 Plate-Figures. Philadelphia: The Blakiston Company, 1948.

While of no great value to the practicing physician or medical student, this text should prove excellent study material for the undergraduate or pre-medical student looking forward to future professional courses. The main purpose of the book is to set forth a plan for the orderly study of a typical mammal, and this it accomplishes in commendable fashion. The type and printing are first-rate and the index is comprehensive and well-organized. The binding is sturdy and the 124 illustrations, including the 8 Plate-Figures, are well-chosen.

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Clinical Biochemistry. By Abraham Cantarow, M.D., and Max Trumper, Ph.D. Fourth edition, cloth, 642 pp., with 38 figures and 22 tables. W. B. Saunders Company, Philadelphia and London, 1949. $8.00.

It is not often that medical text gains wide recognition and enjoys the favor of both student and clinician, but **Clinical Biochemistry** is one of the rare exceptions. In this new edition, the authors, in translating current biochemical knowledge into clinical practice—and in indicating the application of biochemistry in diagnosis and treatment, have kept abreast of the rapid advances in the past few years. Many of the chapters, including those on experimental diabetes and renal and respiratory regulation of acid base balance, have been extensively revised; and there are additional new topics such as: the crush syndrome, alarm reaction, potassium in the treatment of diabetic coma, etc. The print and type are good, the index is excellent, and at the end of each chapter is a comprehensive bibliography. The book is urgently recommended to all men of the medical profession, especially to those "physiology minded."

SCHOOL NOTES AND NEWS

FACULTY

The **Quarterly** wishes to take this opportunity to welcome Dr. Elie Pierre Leroy to the Chicago Medical School as Associate in Pathology.

A native of Jacmel, Haiti, Dr. Leroy received his degree in medicine in 1941 from the Faculte de Medecine et de Pharmacie in Port-au-Prince, Haiti, after interning in the Port-au-Prince Hospital General. He came to America in 1942 and served as an interne at the Provident Hospital in Chicago for one year. In 1943, Dr. Leroy accepted a residency in pathology at Provident Hospital which was supplemented by a fellowship in Pathology at Cook County Hospital. Upon the termination of this residency in 1945, Michael Reese Hospital in Chicago claimed his services as Junior Assistant in Pathology. While at Michael Reese, Dr. Leroy was also an instructor in pathology at the University of Illinois, College of Medicine. After the period of 1947-48, during which Dr. Leroy served as the Director of Laboratories of the Kankakee State Hospital in Illinois, he returned to Haiti to accept the position of Professor of Pathology at the Faculte de Medecine and Director of the Laboratories at the Hospital General of Port-au-Prince. After returning to this country in the latter part of 1948, he was appointed Assistant Pathologist at Mount Sinai Hospital in Chicago and an Associate in Pathology at the Chicago Medical School.

Besides being a member of the Chicago Pathological Society, Dr. Leroy is a member of the Advisory Board of the Haitian Medical Society and is also a Diplomate of the American Board of Pathology—Section of Pathological Anatomy.

Dr. Leroy has published the following articles:

Aronson, A., and Leroy, E. P.: "Electrocardiagraph Findings in Leukemia" Blood, The Journal of Hematology, Vo. II:4 (July, 1947).

Saphir, Otto, and Leroy, Elie P.: "Aneurysm of the Mitral Valve in Subacute Bacterial Endocarditis," American Journal of Pathology, Vol. XXIV:1 (January, 1948).

Department of Anatomy

At the present time, Dr. Congdon is completing work on the following project: "Branches of the axillary artery in the Siamese and new methods of analyzing more variable arteries in general," in collaboration with Soodchitra Sangivichien, Walter Harrison Jr., Salvatore Yanitelli and Max R. Waller.

Textbood descriptions of the axillary branches are inadequate for the purposes of the medical student and the clinician because of the extreme variability of some parts of these vessels. Material is being collected for the study of the Caucasian.

The second object of the investigation is to apply experiences acquired in studying the various axillary arterial patterns of the Siamese to the development of methods for analyzing the more variable arteries in general.

Another project is: "Parasympathetic ganglia in the pharynx," by Dr. E. E. Congdon and Mr. Max Waller.

Because of the supposed parasympathetic innervation of the oro- and laryngo-pharynx, presence of ganglia in the wall seem probable. The senior author has seen them in two regions of the human pharynx. A ganglion seems to have been reported only for the tonsillar sinuses of the human pharynx and that in a brief note.

Dr. L. H. Strong is working on a project which will demonstrate the force components in naso-pharyngeal occlusion. There is no integrated statement in the literature of naso-pharyngeal occlusion that conforms to the known architecture during deglutition. Dr. Strong is interested in the seriation of the forces and how they act. In this study, begun in 1940, facial and muscle relations are indicated by the use of cross section dissections from which a three-dimensional picture ensues.

At the present time, Dr. J .M. Essenberg is working on the following projects: 1. The effect of nicotine on general body development and formation of cancer in the lung. 2. The effect of nicotine on the development and function of the gonads. 3. The growth and development of germ cells. 4. Coronary circulation.

The importance of the hypothalamus in the integration of sex behavior and possibly in the control of secretion of gonadotrophic hormones has long been recognized. In the last decade evidence has been presented that this control is localized in the anterior hypothalamus and that a pathway passes caudally from this region. In 1942, Dr. Clark demonstrated that if this pathway was located in the medial portion, as evidence indicated, it must lie very superficially on the base of the brain. Experiments are now being conducted by Dr. George Clark to check this possibility. Miss Margaret M. Powers, formerly at the Medical College of the State of South Carolina, is now here developing this technique. This investigation is being supported by a grant from the Committee for Research in Problems of Sex, National Research Council.

Dr. H. S. Fish is at the present time, studying connective tissue growth in the infant rat. Studies will be with unfixed and unstained tissues mainly; but with fixed and stained preparations to verify the **in vivo** observations. This study will observe the methods of growth of the fibers and their origin relative to the observations through the microscope.

Department of Biochemistry

Dr. Richard G. Roberts is completing a project on the effect of oral administration of insulin to control diabetes. The drug, which is an insulin compound, is still in the experimental stage. Further experimentation is necessary before this compound can become generally available. This preparation has the potentiality of lowering the fasting diabetic blood glucose level for a period of 48 hours. The chemical is in the process of being patented and its manufacture will be licensed by the Chicago Medical School Foundation.

At the present time, this compound has caused a marked lowering of the blood sugar level in rabbits for a period of 48 hours without producing the effects of insulin shock. The drug is next to be tested on dogs and finally on humans. The chemical name of the compound is Ammano-insulin-choline-chloride-hemochromogen, with a trade name of "Antidiabetic."

Dr. L. J. Saidel is undertaking a study of the functional groups on the intact protein molecule by a series of organic reactions in various solvents.

Dr. Saidel is also studying the process of protein synthesis in the living organism.

At the present time, Dr. A. R. Goldfarb is working on: 1. Determination of the composition and osmotic properties of the insulin-hemin-choline complex and the isolation of the active principle of the complex. 2. Study of the structure of proteins by analysis of partial hydrolysates. 3. Electrophoretic examination of serum proteins in various pathological conditions. (With Dr. Atlas). 4. Studies of the proteins of human erythrocyte with a view to establishing mechanisms for agglutination and hemolysis reactions. (With Dr. Scheff.)

Dr. W. Dasler has initiated experiments which are designed to determine the nature of the toxic principle which is responsible for the condition known as lathyrism. Also, under Dr. Dasler's direction, a study of the factors involved in the production of rickets in the rat is under way.

Department of Pathology

Dr. I. Davidson has announced that there will be an increasing emphasis on gross tissue in the pathology course. In order to facilitate this, a new very efficient refrigerator has been installed which will permit collection of fresh specimens from the various hospitals.

Department of Microbiology and Public Health

Dr. Irwin S. Neiman will address the American Public Health Association on October 26 in New York City. The subject of his address will be "The Relative Stability of the Schick and Dick Tests."

Department of Physiology

Research Problems in Progress:

"The relation of thyroxin and steroid sex hormones to the formation of pigment." Dr. Ben B. Blivaiss.

"The relation of diabetes to the metabolism of thiamine." "The metabolic effects of pancreatic extracts from alloxan diabetic dogs." Drs. P. P. Foa, J. A. Smith and Miss Harriet Weinstein.

"The action of certain autonomic drugs in animals and man." "The relation of the sympathetic nervous system to peptic ulcer in man." "The role of the sympathetic nervous system in the production of gastric ulcers in animals." Dr. A. H. Ryan.

"Treatment of chronic uremia by lavage on isolated intestinal loops with a physiological solution." Dr. Howard Sloan.

"Fundamental action of digitalis as shown by oxygen consumption, carbon dioxide production, etc., on the isolated beating heart; studies of thiamine toxicity, particularly as it affects the stimulating action of acetylcholine on the heart; relation between thiamine and insulin on carbohydrate metabolism of isolated tissues; toxic effects of ergot products; toxicity of mesantoin, and anticorrulsant." Dr. Jay A. Smith.

Department of Psychiatry

Dr. Paul J. Jordan, Assistant Professor of Psychiatry, has been appointed director of the Flint State Child Guidance Clinic, Flint, Michigan, effective September 1, 1949.

Department of Surgery

Dr. Eugene J. Chesrow, Professor of Surgery, has been appointed Exchange Professor in Surgery to the University of Haiti. He recently received the Legion of Honor and Merit medal and citations of the government of Haiti. The decoration, highest award of the Haitian government, was given in recognition of a long period of surgical work among the poor of Haiti, and for service in fostering Haitian-American relationships.

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ALUMNI

The Executive Committee of the Alumni Association has been in session several times in recent months on a number of important matters including the drafting of a new constitution and by-laws and a discussion of matters relating to the status of the older Chicago Medical School graduates.

A meeting of the Alumni Assembly is planned for early September at which time there will be a selection of nominees for representation on the Board of Trustees.

The officers of the Alumni Association are: Dr. Henry A. Smith, president; Dr. Henry Du Vries, vice-president; Dr. Morris Fox, secretary; and Dr. Frank Lawler, treasurer.

Class of 1932

Dr. Martin F. Heigden has been appointed Director of the Hospital of the Tucson Medical Center.

Class of 1936

Dr. Nathan Mann, announces the removal of his office from 1234 Third Street to the Murray Building, 1733 Brownlee Boulevard in Corpus Christi, Texas.

Class of 1937

The QUARTERLY is happy to learn of the marriage of Dr. George R. Hamilton,

on June 18, 1949 in Highland, Indiana, to the former Miss Ruby Owens.

Class of 1939

Congratulations to Dr. Frank C. Lawler upon his marriage to Miss Patricia Mary on June 25, in Chicago.

Class of 1940

It's a son, Barry John, born July 27, for Dr. and Mrs. Adio A. Freeman in Los Angeles.

Class of 1943

Dr. and Mrs. Jack Elliot Clare announce the birth of a son, Kenneth Michael, on August 5, 1949.

Class of 1945

Dr. Louise Tumarkin announces the opening of her office at 7041 West Higgins Road in Chicago.

Congratulations on the recent arrival to the household of Dr. and Mrs. Donald Morrison of Leon Sandor on July 14, 1949.

Drs. Burton W. Rockliff and Earl Zanove announce the opening of joint offices at the Norwood Clinic, 7820 West Higgins Road, Chicago 31, Illinois.

Class of 1946

Mr. and Mrs. John Shivley announce the birth of a son, Joel Cuthbert, on July 30. Mrs. Shivley is the former Normabelle Helman, of the Class of 1946.

Class of 1947

Dr. Bernard Z. Reizner announces the opening of his office at 8505 Fernald Avenue, Morton Grove, Illinois.

Dr. Frank M. Rampello announces the opening of his office at 542 A Willoughby Avenue, Brooklyn, New York.

Dr. Louis J. Polskin is now a practicing physician and surgeon at 1304 South Florida Avenue, Lakeland, Florida. He is a member of the Polk County Medical Society and on the staff of the Morrell Memorial Hospital.

Class of 1948

Dr. Stanley Beckerman has opened his office at 152 Main Street, Waterville, Maine.

Dr. Jerome A. Ehrlich announces the opening of his office for the practice of medicine and surgery at 80 Caryl Avenue, Yonkers, New York.

The QUARTERLY Staff and the Alumni Association pay their respects to these honored dead:

Dr. John Pishotta, Class of 1923, deceased June 8, 1948; age 53.

Dr. Fred S. Saruk, Class of 1936, deceased March 14, 1948; age 43.

Dr. F. B. Steinbeg, Class of 1934, deceased March 16, 1949; age 38.

Dr. Frank J. McDonough, Class of 1906 (Jenner Medical College).

Dr. Lawrence G. Gould, Class of 1940, deceased August 7, 1949.

STUDENT

Class of 1950

Best of luck to Phil Oransky who will make Rhoda Hershander of New York his bride on September 25, 1949.

Congratulations to the Safadis, Millers and Elegants who have had recent additions to their families; and moral support goes to Lawrence Moser, Leonard Grayson and Seymour Filman whose wives are expecting in the very near future.

Our heartfelt sympathy to the Leonard Gordons in the loss of his sister.

Class of 1951

To put the finishing touches on a well-earned summer vacation, Israel Siegal will marry Molly Danishefsky of Bayonne in the early part of September.

Class of 1952

Congratulations are in order for Henry Rosner who will marry Miss Lillian Stern on September 20, 1949 in New York, and to Ed Weissman who will wed Miss Esther Brackarsh of Long Island, New York on September 10, 1949.

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FRATERNITY

Phi Beta Pi

In the spring of this year a group of students interested in organizing a national medical fraternity met with Dr. Leslie B. Arey of Northwestern University, and members of the Phi Beta Pi chapters of Illinois, Northwestern and Loyola. Following this meeting, the "Beta Mu Society," consisting of 23 members, was formed. The national chapter of Phi Beta Pi was petitioned for a char-

ter and the national officers gave their unanimous approval. The group now awaits the vote of all the individual chapters. This approval is expected when the various fraternity chapters meet in September.

The Beta Mu Society is sponsored by Dr. Essenberg, Dr. Strong and Dr. Robinson of the Chicago Medical School faculty. The present officers are Alson Modert, president; Murray Brown, vice-president; Walter Bose, secretary; and Chester Meyers, treasurer.

Phi Delta Epsilon

On August 20, 1949, the Beta Tau chapter of Phi Delta Epsilon fraternity was installed at the Chicago Medical School. The installation proceedings took place at the Chicago Furniture Mart, and were conducted by Dr. B. Edgar Spiegal, Executive Secretary of Phi Delta Epsilon. Dr. Speigel was assisted by Dr. Harry J. Isaacs, Professor of Medicine; Dr. Earl Greene, Professor of Surgery; Dr. Harry Rolnick, Professor of Urology; and Dr. Leo Zimmerman, Professor of Surgery, all faculty members of the Chicago Medical School.

Also present at the installation proceedings were members of the Chicago Area Graduate Club of Phi Delta Epsilon, who sponsored a dinner in honor of the occasion.

Officers of the new chapter are: Lawrence Ravich '50, Consul; Phillip Oransky '50, Scribe; Lawrence Moser '50, Chancellor. Other charter members include: Milton Fox '50, Marvin Jaffee '50, Irwin S. Morse '50, Joshua Magidson '50; Alvin Z. Tucker '50, and Edward Weissman '52.

Phi Lambda Kappa

Along with Chicago Medical School, the Alpha Rho Chapter of Phi Lambda Kappa has gone on a 12-month schedule. Although all our fraters in the Junior Class are now on a well-earned vacation, we have carried on with several business meetings, cultural and social affairs.

Medical movies sponsored by the fraternity will again be resumed in the fall. These are open to the student body and to the faculty of the school.

We are looking forward to welcoming our vacationing fraters and the new freshman class in October.

At present a business, cultural and social program for the coming year is being planned.

The fraternity wishes to welcome the new organizations, recently formed, into the school, and we wish them every success in the future. It is our sincere hope that there can be co-operation between the organizations to make for a more coordinated program of student affairs.

The officers under whose guidance the fraternity will function this years are: Melvin Ehrich, president; Bernard Rosenfeld, vice-president; George Kaufman, secretary; Melvin Pick, treasurer; and Maurice Sherman, Alumni Secretary.

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EDITOR'S NOTE

The new format was designed to conform in size with most other medical journals for readability, and efficiency. Advertising has been discontinued. The subscription policy has also been discontinued and for the present the QUARTERLY will be distributed to all alumni without charge.

We will attempt to include in each issue two or three articles of clinical interest, one to two articles of pre-clinical interest, one alumni and one student article, and one clinical-pathologic conference. Discussions of individual articles by qualified men will be included whenever possible (with permission of the author). All articles will be subject to critical review by qualified men selected by the Editorial Board and will be accepted or rejected upon their recommendation.

The QUARTERLY invites short items by the faculty and alumni based upon observation, clinical experience, etc. for inclusion in "Current Comment." By-line will be given unless otherwise indicated by the author. Conditions outlined under "Instructions to Contributors" will apply here.

The QUARTERLY staff is composed of volunteer students. The Editorial Board is selected by the Dean of the School.